Antiulcer Agents. 2. Gastric Antisecretory, Cytoprotective, and Metabolic Properties of Substituted Imidazo[1,2-*a*]pyridines and Analogues†

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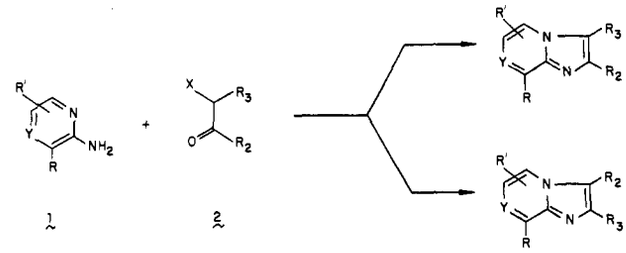
The search for a successor to 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, Sch 28080 (**27**), a compound that exhibits gastric antisecretory and cytoprotective properties and has undergone clinical evaluation as an antiulcer agent, has culminated in the identification of four related compounds that exhibit pharmacologic profiles similar to that of **27**. In three of these potential successors an amino group functions as a surrogate for the 3-cyanomethyl substituent of the prototype. The present work concerns, in addition to an evaluation of the structure–activity relationships of a series of analogues of **27**, preliminary studies of the pharmacodynamics and metabolism of **27**, performed with the aid of cyano carbon labeled versions of the drug (^{13}C labeled; **28**; ^{14}C labeled, **29**). These studies have shown that **27** is well-absorbed and extensively metabolized and that the major metabolite of **27** is the thiocyanate anion. A similar study performed on 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, labeled at the 3-position with carbon-13 (**41**) or carbon-14 (**42**), revealed that this compound, which has an antisecretory/cytoprotective profile comparable to that of **27**, is also metabolized to thiocyanate anion, although this must occur via a different mechanism. The chemistry section includes a discussion of the potential sites of protonation of the pharmacologically similar 3-amino analogue **40** and the structurally related imidazo[1,2-*a*]pyrazine **67**. Predictions based on charge density and protonation product stabilities are presented. That N_1 is the site of protonation in these analogues has been definitively demonstrated by X-ray crystal structue analysis, which also unequivocally established the assigned imidazo[1,2-*a*]pyrazine ring structure.

As part of our efforts to identify novel antiulcer agents, a series of substituted imidazo[1,2-*a*]pyridines has been reported that represents a new class of antiulcer agents.[1] The compounds described are not histamine (H_2) receptor antagonists nor are they prostaglandin analogues, yet they exhibit both gastric antisecretory and cytoprotective activities in animal models. The mechanism of gastric antisecretory activity may involve inhibition of the H^+/K^+-ATPase enzyme.[2,3]

Structure–activity studies led to the identification of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine, Sch 28080 (**27**), which was evaluated clinically.[4,5] However, further development of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**27**) to become an antiulcer drug has been suspended due to some toxicological problems.[6] Hepatic changes observed in animals during continued drug safety studies identified the liver as a target organ of toxicity. Concomitant with this finding was the observation of elevated serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels in human volunteers during a rising dose tolerance study.

The present work concerns the search for a successor to **27** by means of a structure–activity study, supported by an investigation of the absorption and metabolic distribution of **27**. Two compounds that emerged from this process are 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**40**) and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**). The structures of these compounds have been established unequivocally, and a preliminary comparative study of the metabolism of **27** and **40** has been completed. On the basis of considerations discussed in the text, 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**), which exhibits an antisecretory and cytoprotective profile comparable to that of **27**, is expected to undergo a different metabolic disposition, which may significantly alter its potential for exhibiting the toxic properties manifested by **27**.[7]

Scheme I. General Synthesis of Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines



Chemistry

Condensation of substituted 2-aminopyridines and 2-aminopyrazines with α-halo carbonyl intermediates results in the formation of substituted imidazo[1,2-*a*]pyridines[8] and imidazo[1,2-*a*]pyrazines,[9] respectively. When unsymmetrical carbonyl compounds are used, two isomeric products are possible depending upon which nitrogen atom of the pyridine or pyrazine initiates the reaction (Scheme I). The regiospecificity of the direction of ring closure in the imidazopyridine-forming reaction has been established previously,[1] and the reaction of other substituted 2-

† Dedicated to Drs. Robert and Gloria Lyle on the occasion of their 40th anniversary.

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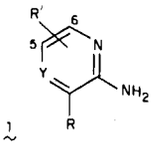
Table I. Substituted 2-Aminopyridines and 2-Aminopyrazines 1



no.	R	R′	Y	mp, °C	recrystn solvent	yield, %	formula	anal.	ref[a]
1a	$PhCH_2O$	H	HC					C, H, N	*b*
1b	$PhCH_2O$	H	CH_3C	oil		73	$C_{13}H_{14}N_2O$	C, H, N	Ex
1c	$PhCH_2O$	5-CH_3	HC	75–76	EtOAc–hexanes	56	$C_{13}H_{14}N_2O$	C, H, N	Ex
1d	$PhCH_2O$	6-CH_3	HC	100–102	CH_3OH	68	$C_{13}H_{14}N_2O$	C, H, N	Ex
1e	$PhCH_2NH$	H	HC						1
1f	$PhCH_2CH_2$	H	HC						1
1g	H	6-$PhCH_2CH_2$	HC						1
1h	H	H	$PhCH_2CH_2C$						1
1i	CHO	H	HC						19
1j	Cl	H	N						20
1k	$PhCH_2O$	H	N	68–74		60	$C_{11}H_{11}N_3O \cdot {}^1/_2H_2O$	C, H, N	Ex

[a] Ex = experimental procedure described. [b] Available from the Aldrich Chemical Co.

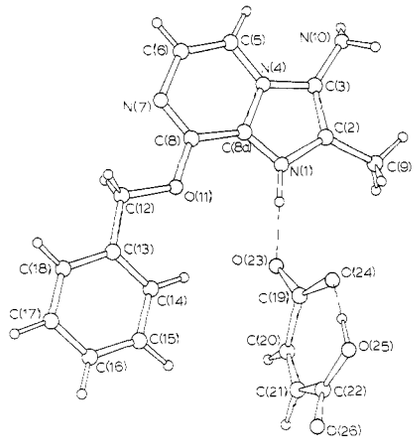


Figure 1. Structure and solid-state conformation of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**) as its hemimaleate salt.

aminopyridines with unsymmetrical α-halo carbonyl compounds was presumed to follow the same course. The direction of closure of substituted 2-aminopyrazines with unsymmetrical α-halo carbonyl intermediates was unequivocally established by single crystal X-ray analysis of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyrazine (**67**), Figure 1, which was derived from 2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**7**).

The substituted imidazo[1,2-*a*]pyridines and imidazo-[1,2-*a*]pyrazines (Table III) were prepared from the substituted 2-aminopyridines and -pyrazines (Table I) and the α-halo carbonyl intermediates (Table II) by following the general methods and specific experimental procedures described.

Method A. Condensation of the appropriately substituted 2-aminopyridine or -pyrazine (**1**) with the appropriate α-halo carbonyl intermediate (**2**) gave the corresponding substituted imidazo[1,2-*a*]pyridines **3–5**, **8**, **30–34**, and **87–89** and imidazo[1,2-*a*]pyrazines **6** and **7**, respectively.

Method B. Alkylation of 8-hydroxy-2-methylimidazo-[1,2-*a*]pyridine (**11**) with 3-thienylmethyl bromide[10] gave 2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (**12**).

Method C. Treatment of the appropriately substituted 2-aminopyridine or -pyrazine (**1**) with the appropriate aldehyde in the presence of sodium bisulfite and sodium cyanide gave directly the corresponding substituted 3-aminoimidazo[1,2-*a*]pyridines **40**, **44–48**, and **61–64** and substituted 3-aminoimidazo[1,2-*a*]pyrazine **67**, respectively.

Via method C, treatment of 2-amino-3-(phenylmethoxy)pyridine (**1a**) with acetaldehyde in the presence of sodium bisulfite and [^{13}C]sodium cyanide or [^{14}C]sodium cyanide gave [3-^{13}C]-3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**41**) and [3-^{14}C]-3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**42**), respectively.

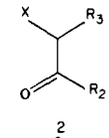
Method D. Nitrosation of 8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (**13**) with *n*-butyl nitrite followed by zinc and acetic acid reduction of the intermediate nitroso compound gave 3-amino-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**43**). The substituted imidazo[1,2-*a*]pyridines **49–55**, **58**, and **60** were prepared by using method D.

Method E. Treatment of 2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (**5**) with *n*-butyl nitrite followed by stannous chloride reduction gave 3-amino-2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]-pyridine (**56**). Via method E, the substituted 3-aminoimidazo[1,2-*a*]pyridines **59** and **63** were prepared.

Method F. Nitrosation of the appropriately substituted imidazo[1,2-*a*]pyridine or imidazo[1,2-*a*]pyrazine with sodium nitrite and acetic acid and subsequent zinc and acetic acid reduction of the nitroso intermediate gave the corresponding substituted 3-aminoimidazo[1,2-*a*]pyridines **57**, **65**, and **66** and substituted 3-aminoimidazo[1,2-*a*]-pyrazine **67**, respectively. Compound **67** was also prepared by using method C.

Method G. Acylation of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**) and 3-amino-2-

Table II. α-Halo Carbonyl Intermediates **2**



no.	R_2	R_3	X	bp, °C (mmHg)	ref
2a	H	H	Br		*a*, *b*
2b	CH_3	H	Cl		*b*
2c	CH_3	CH_2CN	Cl	83–93 (0.3)	1
2d	CH_3	OCH_3	Br	83–89 (22)	21
2e	CH_3	SCH_3	Cl	93–96 (16)	22, 23
2f	CH_3	CH_3	Br		*c*

[a] Used as the diethyl acetal. [b] Available from the Aldrich Chemical Co. [c] Available from Eastman Kodak Co.

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methyl-8-(2-phenylethyl)imidazo[1,2-a]pyridine (61) with the appropriate acylating agent gave the corresponding substituted N-acyl-substituted imidazo[1,2-a]pyridines 71–77.

Method H. Borane reduction of the appropriately substituted N-acyl-substituted imidazo[1,2-a]pyridines gave the corresponding N-alkyl-substituted imidazo[1,2-a]pyridines 78–80.

Method I. Reductive alkylation of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (40) using the appropriate aldehydes in the presence of sodium cyanoborohydride gave the corresponding N-alkyl-substituted imidazo[1,2-a]pyridines 81–86.

Following the specific experimental procedures described below, we prepared the remaining substituted imidazo-[1,2-a]pyridines 9, 10, 28, 29, 35–39, 41, 42, 70, 90, and 91 and substituted imidazo[1,2-a]pyrazine 68 (Table III).

The site of protonation and N-methylation of the imidazo[1,2-a]pyridine system has been the subject of considerable interest.[11] In fact, several studies of this type have been devoted to demonstrating the aromatic character and planarity of the ring system. Protonation and N-methylation in imidazo[1,2-a]pyridine occur at the nitrogen atom in position 1 (N_1). This observation is predicted by frontier electron density calculations and is demonstrable by studying the peri interaction between a proton at the 8-position and a methyl group substituted on N_1 in the proton magnetic resonance spectrum.[12,13]

Substitution of an amino group at the 3-position of the imidazo[1,2-a]pyridine ring system introduces an alternative site for protonation, N_{10} (as in, for example, compound 40). The situation is further complicated in the amino-substituted imidazo[1,2-a]pyrazines (for example, 67) by the presence of yet another potential site of protonation, N_7. The significance of establishing the site of protonation in these systems is important since it has recently been suggested that compounds of this type specifically compete with potassium ion to inhibit the H^+/K^+-ATPase enzyme in their protonated form.[14]

The comparable basicities of 27, 40, and 67 with approximate pK_a's of 5.5, 5.8, and 4.6, respectively, suggests that the protonation of these systems may occur at a common site.

Comparison of the differences in proton chemical shifts between the base and the proton salt for 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]-pyridine (27), 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-a]pyridine (40), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyrazine (67) (Table IV) indicates that protonation has a comparable effect on the chemical shifts of H-5, H-6, and the 2-methyl group in the three systems, again suggesting that protonation occurs at the equivalent site in all three analogues.

Examination of the nitrogen atom charge densities in the imidazo[1,2-a]pyridine and the imidazo[1,2-a]pyrazine systems calculated by using MINDO/3 or MNDO/2 (Table V) indicates that, regardless of the computational method employed, N_1 is the nitrogen atom of greatest electron density in 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (40), whereas in 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyrazine (67), N_7 is the nitrogen atom of greatest electron density.

Protonation is an equilibrium process and, this being so, the product of the reaction is controlled thermodynamically. Therefore, comparison of the electron densities in the ground states may not be predictive of the site of protonation. A more meaningful analysis would be a comparison of the stabilities of the varous protonated products. Comparison of the heats of formation (Table V) for the various protonated products of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (40) and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]-pyrazine (67) suggests that, in both systems, the most stable protonated product results from protonation at N_1.

The sites of protonation in the imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrazine systems were established unequivocally by single crystal X-ray analysis of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (40) as its hydrochloride salt (40·HCl) and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyrazine (67) as its hemimaleate (67·Mal). Both crystal structures were solved by direct methods.[29a] Full-matrix least-squares refinement of atomic parameters[29b] converged to $R = 0.042$[30] for 40·HCl and $R = 0.038$[30] for 67·Mal. Bond lengths and angles[31] are all in accord with expected values. Views of the solid-state conformations are presented in Figures 2 (supplementary material) and 1 respectively. In both cases, N_1 was established as the site of protonation, a result that is consistent with the calculated stabilities of the protonated products rather than the ground state electron densities. The bonding geometry at the amino substituent, N_{10}, which is involved as a proton donor in the interionic hydrogen bonded interactions in the crystals, is pyramidal in both cations. The packing arrangement in crystals of 40·HCl is illustrated in Figure 3[29b] (supplementary material).

Biological Test Methods

The compounds were evaluated for gastric antisecretory activity in two animal models (Table VI). The pylorus-ligated rat[15] was used as the primary screen to assess antisecretory activity and to identify potentially toxic com-

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(29) (a) All crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programs. The direct methods program MULTAN11/82 was employed. (b) Supplementary material: see the paragraph at the end of the paper.
(30) $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = [\Sigma w(||F_o| - |F_c||)^2/\Sigma w|F_o|^2]^{1/2}$.
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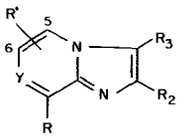
Table III. Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines



no.	R_2	R_3	R	R′	Y	synth meth	mp, °C	recrystn solvent	yield, %	formula	anal.
3	CH_3	H	$PhCH_2O$	H	CH_3C	A	151–154	CH_3OH–Et_2O	86	$C_{16}H_{16}N_2O$·HCl	C, H, N, Cl
4	CH_3	H	$PhCH_2O$	5-CH_3	HC	A	57–59	Et_2O-hexanes	13	$C_{16}H_{16}N_2O$	C, H, N
5	CH_3	H	$PhCH_2NH$	H	HC	A	53–55	Et_2O–hexanes	24	$C_{15}H_{15}N_3$	C, H, N
6	CH_3	H	Cl	H	N	A	113–123		37	$C_7H_6ClN_3$	C, H, N, Cl
7	CH_3	H	$PhCH_2O$	H	N	A	99.5–101.5		43	$C_{14}H_{13}N_3O$	C, H, N
8	CH_3	H	CHO	H	HC	A	140–143	(*i*-Pr)$_2$O	78	$C_9H_8N_2O$	C, H, N
9	CH_3	H	CH_2OH	H	HC	Ex	132–137	dimethoxyethane	93	$C_9H_8N_2O$	C, H, N
10	CH_3	H	CH_2OPh	H	HC	Ex	65–67	Et_2O–hexanes	30	$C_{15}H_{14}N_2O$	C, H, N
11	CH_3	H	OH	H	HC	*b*					
12	CH_3	H	3-thienyl-CH_2O	H	HC	B	134–135	EtOAc	52	$C_{13}H_{12}N_2OS$	C, H, N
13	H	H	$PhCH_2O$	H	HC	*b*					
14	CH_3	H	$PhCH_2O$	H	HC	*b*					
15	CH_3	H	2-$FC_6H_4CH_2O$	H	HC	*b*					
16	CH_3	H	4-$FC_6H_4CH_2O$	H	HC	*b*					
17	CH_3	H	4-$ClC_6H_4CH_2O$	H	HC	*b*					
18	CH_3	H	4-$CF_3C_6H_4CH_2O$	H	HC	*b*					
19	CH_3	H	$PhCH_2CH_2O$	H	HC	*b*					
20	CH_3	H	2-$PyCH_2O$	H	HC	*b*					
21	CH_3	H	2-thienyl-CH_2O	H	HC	*b*					
22	CH_3	H	$PhCH_2CH_2$	H	HC	*b*					
23	CH_3	H	H	6-$PhCH_2CH_2$	HC	*b*					
24	CH_3	H	$PhCH_2S$	H	HC	*b*					
25	CH_3	H	PhO	H	HC	*b*					
26	CH_3	$CH_2N^+(CH_3)_3I^-$	$PhCH_2O$	H	HC	*b*					
27	CH_3	CH_2CN	$PhCH_2O$	H	HC	*b*					
28	CH_3	$CH_2{}^{13}CN$	$PhCH_2O$	H	HC	Ex	161–162	EtOAc–Et_2O	74		*c*
29	CH_3	$CH_2{}^{14}CN$	$PhCH_2O$	H	HC	Ex		EtOAc–Et_2O			*d*
30	CH_3	CH_3	$PhCH_2O$	5-CH_3	HC	A	105–107	Et_2O–hexanes	11	$C_{17}H_{18}N_2O$	C, H, N
31	CH_3	CH_3	$PhCH_2O$	6-CH_3	HC	A	115–116	Et_2O	56	$C_{17}H_{18}N_2O$	C, H, N
32	CH_3	CH_3	$PhCH_2O$	H	CH_3C	A	187–188	EtOH–Et_2O	70	$C_{17}H_{18}N_2O$·HCl	C, H, N, Cl
33	CH_3	CH_2CN	$PhCH_2O$	5-CH_3	HC	A	218–220	CH_3CN	40	$C_{18}H_{17}N_3O$·HCl	C, H, N
34	CH_3	CH_2CN	$PhCH_2O$	H	CH_3C	A	161–162	CH_3OH–EtOAc	32	$C_{18}H_{17}N_3O$·HCl·$^1/_2H_2O$	C, H, N, Cl
35	CH_3	H	OH	H	HC, 5,6,7,8-H_4	Ex	140–152		100	$C_8H_{12}N_2O$·HCl	
36	CH_3	H	$PhCH_2O$	H	HC, 5,6,7,8-H_4	Ex	oil		52	$C_{15}H_{18}N_2O$	
37	CH_3	$CH_2N(CH_3)_2$	$PhCH_2O$	H	HC, 5,6,7,8-H_4	Ex	68–70		78	$C_{18}H_{25}N_3O$	C, H, N
38	CH_3	$CH_2N^+(CH_3)_3I^-$	$PhCH_2O$	H	HC, 5,6,7,8-H_4	Ex	126 dec		72	$C_{19}H_{28}IN_3O$	
39	CH_3	CH_2CN	$PhCH_2O$	H	HC, 5,6,7,8-H_4	Ex	131.5–134.5		20	$C_{17}H_{19}N_3O$·0.3H_2O	C, H, N
40	CH_3	NH_2	$PhCH_2O$	H	HC	C or F	205–206	CH_3OH–EtOAc	28	$C_{15}H_{15}N_3O$·HCl	C, H, N, Cl
41	CH_3	NH_2	$PhCH_2O$	H	HC, $^{13}C_3$	Ex	205–206	CH_3OH–EtOAc	28		*e*
42	CH_3	NH_2	$PhCH_2O$	H	HC, $^{14}C_3$	Ex		CH_3OH–EtOAc			*f*
43	H	NH_2	$PhCH_2O$	H	HC	D	209–210	CH_3OH–EtOAc	12	$C_{14}H_{13}N_3O$·HCl	C, H, N
44	CH_3CH_2	NH_2	$PhCH_2O$	H	HC	C	109–110	EtOAc–hexanes	16	$C_{16}H_{17}N_3O$	C, H, N
45	*n*-C_3H_7	NH_2	$PhCH_2O$	H	HC	C	88–89	(*i*-Pr)$_2$O	12	$C_{17}H_{19}N_3O$	C, H, N
46	*i*-C_3H_7	NH_2	$PhCH_2O$	H	HC	C	167–169	EtOAc–hexanes	11	$C_{17}H_{19}N_3O$	C, H, N
47	*n*-C_4H_9	NH_2	$PhCH_2O$	H	HC	C	115–117	(*i*-Pr)$_2$O	10	$C_{18}H_{21}N_3O$	C, H, N
48	*t*-C_4H_9	NH_2	$PhCH_2O$	H	HC	C	173–175	EtOAc	14	$C_{18}H_{21}N_3O$	C, N, N
49	CH_3	NH_2	2-$FC_6H_4CH_2O$	H	HC	D	151–152.5	$CHCl_3$–Et_2O	70	$C_{15}H_{14}FN_3O$·$^1/_4H_2O$	C, H, N, F
50	CH_3	NH_2	4-$FC_6H_4CH_2O$	H	HC	D	165–166	$CHCl_3$–Et_2O	65	$C_{15}H_{14}FN_3O$·$^1/_4H_2O$	C, H, N, F
51	CH_3	NH_2	4-$ClC_6H_4CH_2O$	H	HC	D	156–158	$CHCl_3$–Et_2O	70	$C_{15}H_{14}ClN_3O$·$^1/_4H_2O$	C, H, N, Cl
52	CH_3	NH_2	4-$CF_3C_6H_4CH_2O$	H	HC	D	210–211 dec	EtOH–$CHCl_3$	40	$C_{16}H_{14}F_3N_3O$·$^1/_2H_2O$·2HCl	C, H, N, Cl

53	CH_3	NH_2	2-$PyCH_2O$	H	HC	D	120–121 dec	$CHCl_3$–EtOAc	30	$C_{14}H_{14}N_4O$	C, H, N
54	CH_3	NH_2	2-thienyl-CH_2O	H	HC	D	147–149	$CHCl_3$–EtOH	40	$C_{13}H_{13}N_3OS$	C, H, N, S
55	CH_3	NH_2	3-thienyl-CH_2O	H	HC	D	157–158	$PhCH_3$	33	$C_{13}H_{13}N_3OS$	C, H, N, S
56	CH_3	NH_2	$PhCH_2NH$	H	HC	E	145–155	EtOAc–hexanes	24	$C_{15}H_{16}N_4$	C, H, N
57	CH_3	NH_2	$PhCH_2S$	H	HC	F	132–134	EtOAc–Et_2O	41	$C_{15}H_{15}N_3S$	C, H, N, S
58	CH_3	NH_2	$PhCH_2CH_2O$	H	HC	D	138–140 dec	CH_3CN–*i*-PrOH	35	$C_{16}H_{17}N_3O \cdot HCl \cdot {}^1/_4H_2O$	C, H, N, Cl
59	CH_3	NH_2	PhO	H	HC	E	135–136	EtOAc–CH_2Cl_2–hexanes	28	$C_{14}H_{13}N_3O$	C, H, N
60	CH_3	NH_2	CH_2OPh	H	HC	D	197–199 dec	EtOAc–Et_2O	40	$C_{15}H_{15}N_3O \cdot 2HCl \cdot {}^1/_2H_2O$	C, H, N, Cl
61	CH_3	NH_2	$PhCH_2CH_2$	H	HC	C	74.5	CH_3OH–EtOAc	48	$C_{16}H_{17}N_3 \cdot HCl \cdot CH_3OH \cdot {}^1/_4H_2O$	C, H, N, Cl
62	CH_3	NH_2	H	H	$PhCH_2CH_2C$	C	143–144	EtOAc–hexanes	29	$C_{16}H_{17}N_3$	C, H, N
63	CH_3	NH_2	H	6-$PhCH_2CH_2$	HC	E	120–122	1-chlorobutane	56	$C_{16}H_{17}N_3$	C, H, N
64	CH_3	NH_2	H	5-$PhCH_2CH_2$	HC	C	236–238	EtOAc–CH_3OH	11	$C_{16}H_{17}N_3 \cdot HCl$	C, H, N
65	CH_3	NH_2	$PhCH_2O$	6-CH_3	HC	F	141–142	EtOAc–Et_2O	18	$C_{16}H_{17}N_3O$	C, H, N
66	CH_3	NH_2	$PhCH_2O$	H	CH_3C	F	181–183	CH_3OH–$(CH_3)_2CO$	58	$C_{16}H_{17}N_3O \cdot HCl \cdot H_2O$	C, H, N, Cl
67	CH_3	NH_2	$PhCH_2O$	H	N	C or F	134.5–136	EtOAc	20	$C_{14}H_{14}N_4O$	C, H, N
68	CH_3	NH_2	$PhCH_2CH_2$	H	N	Ex	>250	CH_3OH–EtOAc	32	$C_{15}H_{16}N_4 \cdot HCl$	C, H, N, Cl
69	CH_3	CH_2NH_2	$PhCH_2O$	H	HC	*b*					
70	CH_3	$CH_2CH_2NH_2$	$PhCH_2O$	H	HC	Ex	164 dec	CH_3OH–EtOAc	35	$C_{17}H_{19}N_3O \cdot 2HCl$	C, H, N, Cl
71	CH_3	HCONH	$PhCH_2O$	H	HC	G	191–192	CH_3OH–EtOAc	42	$C_{16}H_{15}N_3O_2$	C, H, N
72	CH_3	CH_3CONH	$PhCH_2O$	H	HC	G	170.5–172.5		89	$C_{17}H_{17}N_3O_2$	C, H, N
73	CH_3	CH_3CONH	$PhCH_2CH_2$	H	HC	G	205.5–206.5	CH_3OH–$(i\text{-}Pr)_2O$	63	$C_{16}H_{19}N_3O$	C, H, N
74	CH_3	CH_3O_2C-NH	$PhCH_2O$	H	HC	G	208.5 dec	CH_3OH–EtOAc	34	$C_{17}H_{17}N_3O_3 \cdot HCl$	C, H, N, Cl
75	CH_3	$PhCH_2O_2$CNH	$PhCH_2O$	H	HC	G	177–179 dec		37	$C_{23}H_{21}N_3O_3 \cdot {}^1/_4H_2O$	C, H, N
76	CH_3	$(CH_3)_2NC$-HN	$PhCH_2O$	H	HC	G	125–133	$(i\text{-}Pr)_2O$–CH_2Cl_2	46	$C_{16}H_{20}N_4O \cdot {}^1/_4H_2O$	C, H, N
77	CH_3	CH_3NHC-ONH	$PhCH_2O$	H	HC	G	220.5–222.5 dec	CH_3CN	53	$C_{17}H_{18}N_4O_2$	C, H, N
78	CH_3	CH_3NH	$PhCH_2O$	H	HC	H	193.5–194		76	$C_{16}H_{17}N_3O \cdot HCl$	C, H, N, Cl
79	CH_3	CH_3CH_2-NH	$PhCH_2O$	H	HC	H	191 dec		60	$C_{17}H_{19}N_3O \cdot HCl$	C, H, N, Cl
80	CH_3	CH_3CH_2-NH	$PhCH_2CH_2$	H	HC	H	145–147 dec		45	$C_{18}H_{21}N_3 \cdot HCl$	C, H, N, Cl
81	CH_3	*n*-C_3H_7NH	$PhCH_2O$	H	HC	I	153–155	CH_3OH–EtOAc	48	$C_{18}H_{21}N_3O \cdot HCl$	C, H, N, Cl
82	CH_3	*i*-C_3H_7NH	$PhCH_2O$	H	HC	I	108–110		73	$C_{18}H_{21}N_3O$	C, H, N
83	CH_3	$PhCH_2NH$	$PhCH_2O$	H	HC	I	72 gum		58	$C_{22}H_{21}N_3O \cdot HCl \cdot 0.4H_2O$	C, H, N, Cl
84	CH_3	CH_3CH_2-NH	$PhCH_2O$	H	N	I	126–126.5 dec		32	$C_{16}H_{18}N_4O \cdot HCl$	C, H, N
85	CH_3	$(CH_3)_2N$	$PhCH_2O$	H	HC	I	187 dec		67	$C_{17}H_{19}N_3O \cdot HCl$	C, H, N, Cl
86	CH_3	$(n\text{-}C_3H_7)_2N$	$PhCH_2O$	H	HC	I	120–121.5	CH_3OH–EtOAc	32	$C_{21}H_{27}N_3O \cdot HCl$	C, H, N, Cl
87	CH_3	CH_3O	$PhCH_2O$	H	HC	A	170–172.5 dec		57	$C_{16}H_{16}N_2O_2 \cdot HBr$	C, H, N, Br
88	CH_3	CH_3O	$PhCH_2CH_2$	H	HC	A	149–149.5 dec		87	$C_{17}H_{18}N_2O \cdot HBr$	C, H, N, Br
89	CH_3	CH_3S	$PhCH_2CH_2$	H	HC	A	145 dec	CH_3OH–EtOAc	50	$C_{17}H_{18}N_2S \cdot HCl \cdot {}^3/_8H_2O$	C, H, N, Cl, S
90	CH_3	HO	$PhCH_2CH_2$	H	HC	Ex	229–231 dec	CH_3OH–EtOAc	59	$C_{16}H_{16}N_2O \cdot HBr$	C, H, N, Br
91	CH_3	CH_3CO_2	$PhCH_2CH_2$	H	HC	Ex	*g*	CH_3OH–$(i\text{-}Pr)_2O$	40	$C_{16}H_{18}N_2O_2 \cdot HCl \cdot 0.4H_2O$	C, H, N, Cl

[a] Ex = experimental procedure described. [b] From ref 1. [c] Percent ^{13}C enrichment was 86% as determined by mass spectral analysis. [d] Specific activity: 28.4 μCi/mg. [e] Percent ^{13}C enrichment was 93% as determined by mass spectral analysis. [f] Specific activity: 26.1 μCi/mg. [g] Decomposition occurs over a broad temperature range beginning at approximately 140 °C.

Table IV. Proton Chemical Shift Differences between the Base and Salt of 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (**27**), 3-Amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**40**), and 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**)

	$\Delta\delta$,[a] ppm		
group	**27**	**40**	**67**
2-CH_3	0.18	0.14	0.14
8-$PhCH_2O$	0.12	0.16	0.14
H-5	0.40	0.55	0.53
H-6	0.6	0.7–1.0	0.50
H-7	0.7	0.8–1.1	

[a] $\Delta\delta = \delta$(base) − δ(salt).

pounds. In this test, the compounds were administered at a 40 mg/kg dose intraperitoneally (ip) at the time of ligation and the reduction in acid output was measured at 4 h.

The secondary model was the inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[16] with surgically prepared Heidenhain pouches. Compounds were first administered in intravenous doses of 0.1–5 mg/kg, and reduction in acid output, relative to the non-drug-treated control value in the same animal, was measured. Selected compounds were also tested against histamine in the Heidenhain pouch dog after oral (po) administration of 2–8 mg/kg doses.

The compounds were tested for gastric cytoprotective activity in the rat (Table VI). In this test, the compound was administered orally (po), 1–30 mg/kg, 30 min before oral administration of absolute ethanol. The effect of the compound against ethanol-induced lesions was determined after 1 h.

Drug Metabolism Methods

The study evaluated the time courses of inhibition of histamine-stimulated acid secretion, the concentration of **27** and total radioactivity in the plasma and gastric juice, and the amounts of radioactivity excreted in the urine and feces up to 7 days after dosing.

Three dogs prepared with gastric fistulae were given a 0.2 mg/kg intravenous dose of **29**, and three dogs with Heidenhain pouches were given a 4 mg/kg oral dose of **29**. Following drug treatment, samples of plasma, gastric juice, urine, and feces were collected and their radioactivity was measured. Plasma and gastric juice were analyzed for **27** by HPLC. The gastric juice volume and acid concentration

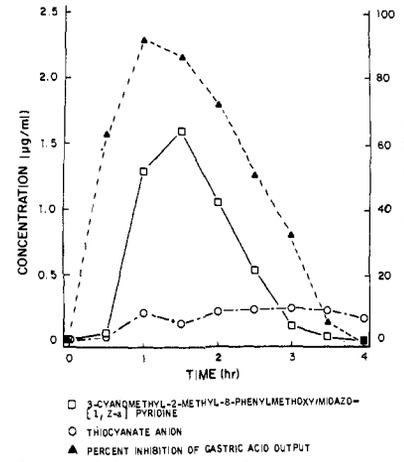


Figure 4. Gastric juice levels of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) (□) and thiocyanate anion (○) and percent inhibition of gastric acid output (▲) following a single intravenous dose (0.2 mg/kg) of **27**.

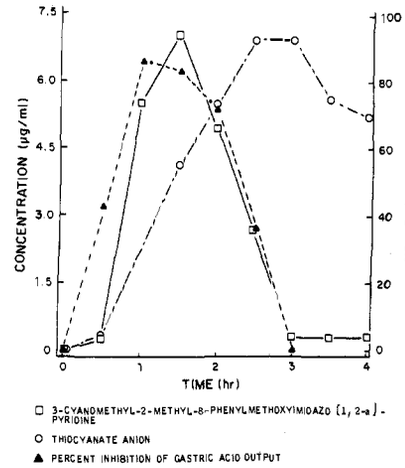
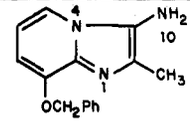
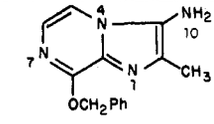


Figure 5. Gastric juice levels of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) (□) and thiocyanate anion (○) and percent inhibition of gastric acid output (▲) following a single oral dose (4.0 mg/kg) of **27**.

were measured, and the acid output was calculated for each dog and expressed as a percent inhibition of gastric acid output relative to a pre-drug control. The results are summarized in Tables VII and VIII and Figures 4 and 5.

Table V. Comparative Heats of Formation for the Protonated Forms of 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**) and 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**)





	40					**67**					
	charge density			site of	heat of	charge density				site of	heat of
computational method	N_1	N_{10}	N_4	protonation	formation, kcal/mol	N_1	N_{10}	N_4	N_7	protonation	formation, kcal/mol
MINDO/3	−0.1827	−0.1516	0.0771		−1.4	−0.1592	−0.1352	0.0855	−0.2894		−4.4
MNDO/2	−0.2066	−0.2050	−0.1460		35.3	−0.1594	−0.1940	−0.1647	−0.3117		40.9
MINDO/3	0.0459	−0.1589	0.1305	N_1	119.4	0.0783	−0.1337	0.1255	−0.2331	N_1	107.5
MNDO/2	−0.1924	−0.2314	−0.1182	N_1	183.9	−0.1547	−0.2052	−0.0861	−0.2488	N_1	191.0
MINDO/3	−0.1517	0.3696	0.1628	N_{10}	136.5	−0.1462	0.3558	0.1873	−0.2653	N_{10}	133.5
MNDO/2	−0.1814	0.1635	−0.1095	N_{10}	208.3	−0.1447	0.1507	−0.0810	−0.3061	N_{10}	213.4
MINDO/3	−0.0158	−0.1264	0.1512	N_4	159.1	−0.0434	−0.1115	0.1216	−0.2588	N_4	169.8
MNDO/2	−0.0791	−0.2301	0.0074	N_4	232.7	−0.0568	−0.2088	−0.0532	−0.3115	N_4	273.4
MINDO/3						−0.0392	−0.1550	0.0431	−0.0770	N_7	111.0
MNDO/2						0.1287	−0.2539	−0.1753	−0.2825	N_7	196.3

3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine labeled with ^{13}C and ^{14}C at the cyano carbon, compounds **28** and **29**, respectively, or 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine labeled with ^{13}C and ^{14}C at the 3-position of the imidazo[1,2-*a*]-pyridine, compounds **41** and **42**, respectively, were given orally (40 mg/kg) to a single dog each, and urine was collected from the dog for 48 h. The isolated urinary metabolites were identified chromatographically and spectroscopically.

Results and Discussion

The discovery of toxicity of our clinical candidate 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, Sch 28080 (**27**), led us to initiate a study directed toward the identification of a successor that would retain the desirable combination of antisecretory and cytoprotective properties of **27**, but devoid of these toxic effects. We also wanted the successor to exhibit a longer duration of action when given orally. The significant disparity between the oral and intravenous gastric antisecretory ED_{50}'s determined for **27** in the histamine-stimulated dog suggested that either **27** is poorly absorbed following oral administration or that **27** suffers significant first-pass elimination and is extensively metabolized.

In order to address the question of bioavailability, we carried out absorption and metabolism studies using [*cyano*-^{14}C]-**27** (**29**). These were done with three dogs prepared with gastric fistulae for intravenous dosing and three with Heidenhain pouches for oral dosing so that gastric fluid could be analyzed to correlate **27** pharmacokinetics with its pharmacodynamics (as determined by the time course of inhibition of gastric acid secretion).

Drug Metabolism

Following intravenous treatment of dogs with **29** (0.2 mg/kg), the mean C_{max} of total radioactivity in plasma (0.14 μg (**27**) equiv/mL) was reached at 1–2 h (Table VII) after dosing. After oral dosing (4.0 mg/kg), the plasma concentration–time profile of radioactivity was similar, with the mean C_{max} (4.0 μg equiv/mL) reached 2–4 h postdose. After both intravenous and oral dosing, the plasma concentrations of unchanged **27** were below the limit of detection of the assay (0.02 μg/mL) at all time points analyzed.

After the intravenous dose of **29**, the concentration of radioactivity in the gastric fluid increased to a mean C_{max} of 2.1 μg equiv/mL at 1.5–2 h after dosing (Table VII); it decreased rapidly so that, at 4 h, the mean gastric juice radioactivity concentration had already declined to 0.78 μg equiv/mL, or 37% of C_{max}. Unchanged-**27** concentrations in gastric juice rose rapidly to a mean C_{max} of 1.6 μg/mL at 1.5 h after intravenous dosing; thereafter its concentration declined rapidly until it was below the assay detection limit 3–3.5 h postdose. Following the oral dose, gastric juice radioactivity concentrations could not be obtained for two dogs, since they did not produce sufficient gastric juice to allow analysis from 1 to 2.5 h after dosing. In the third dog, the only animal that secreted sufficient gastric juice throughout the 4-h collection period, gastric juice radioactivity concentrations increased rapidly to a C_{max} of 35.7 μg equiv/mL at 2.5 h posttreatment; at the end of the collection period (4 h) the concentration was still high (25.2 μg equiv/mL). Unchanged **27** in this dog's gastric fluid reached a C_{max} of 7.0 μg/mL at 1.5 h postdose and declined to 0.3 μg/mL at 3 h after dosing.

Comparison of peak plasma radioactivity levels after the oral and intravenous doses indicates good oral absorption of **29**. The absence of detectable concentrations of **27** and the relatively high concentrations of radioactivity in plasma after both oral and intravenous administration suggest that **27** is rapidly cleared from plasma by metabolism and/or tissue uptake. The data also suggest a significant uptake of radioactivity by the stomach; gastric radioactivity concentrations were over 10 times greater than plasma levels. These observations are similar to our unpublished findings for the rat, where a tissue distribution study showed an extensive uptake of radioactivity by the stomach and intestine, but little uptake in other tissues. More striking were the differences in unchanged-**27** concentrations. This drug was unmeasurable in dog plasma, but reached very high gastric fluid levels; in fact, it was the major component of the radioactivity up to 2 h after dosing.

Since it had thus been established that **27** is well-absorbed, but extensively metabolized in the dog, the metabolism of **27** was investigated. This preliminary study was undertaken so that the role of any metabolites in the pharmacology and toxicity of **27** might be assessed. In addition, definition of the metabolic sites of **27** would assist in designing analogues of **27** exhibiting structural variation that would differentiate their metabolic fate, pharmacokinetics, and bioavailability from that of **27**.

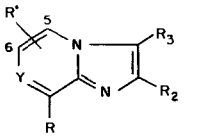
Thin-layer radiochromatography was used to quantitate relative amounts of **27** and metabolites in urine and gastric fluid. Preliminary investigation had shown that the only detectable metabolite in rat urine was a fraction that cochromatographed with the thiocyanate anion. In dog urine, this peak was the major metabolite, accounting for 20.2% of the administered dose. There was also a substantial amount of unchanged drug (30.2% of dose). The only imidazo[1,2-*a*]pyridine metabolite (identified by comparison of R_f values) was 3-(cyanomethyl)-2-methyl-8-hydroxyimidazo[1,2-*a*]pyridine,[1] which accounted for only 0.4% of the dose. Unidentified radioactivity accounted for 5.2% of the dose.

Using **27** labeled with ^{13}C (compound **28**) and ^{14}C (compound **29**) at the cyano carbon, we determined that the major radiolabeled metabolite of **27** was indeed thiocyanate anion. It was isolated from the urine of one dog dosed with **27** that had 45% ^{13}C enrichment and a small amount of ^{14}C enrichment and characterized by ^{13}C magnetic resonance spectroscopy and mass spectral analysis.[18] The ^{13}C-NMR spectrum exhibited a peak with a chemical shift identical with that of standard thiocyanate, δ_{obsd} 134.4 (δ_{SCN} 134.4). The low-resolution mass spectrum determined in the presence of ammonium chloride clearly shows peaks for HSCN at *m/e* 59 and $HS^{13}CN$ at *m/e* 60. The intensity of the *m/e* 60 peak was 46.5% of the *m/e* 59 peak, which is in excellent agreement with the ^{13}C enrichment of the dose. Furthermore, high-resolution mass spectral data confirmed that the isolated metabolite was thiocyanate: calcd for HSCN 58.9830, obsd 58.9831; calcd for $HS^{13}CN$ 59.9863.

Thiocyanate anion presumably arises from oxidative decyanation of the 3-cyanomethyl function followed by conversion of the cyanide anion formed to thiocyanate anion by the enzyme rhodanese (Scheme II). The detoxification of cyanide by rhodanese appeared to be extremely efficient, as no cyanide could be detected in the urine, plasma, or gastric juice of dogs or rats.

Thin-layer radiochromatography established that only **27** and thiocyanate could be detected in dog gastric juice. Concentration–time profiles of **27** and thiocyanate in gastric juice were plotted together with the pharmacodynamic data to determine if a pharmacokinetic–pharmacodynamic relationship existed. (Thiocyanate was determined indirectly by subtracting the amount of **27** from the

Table VI. Gastric Antisecretory and Cytoprotective Activities of Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines

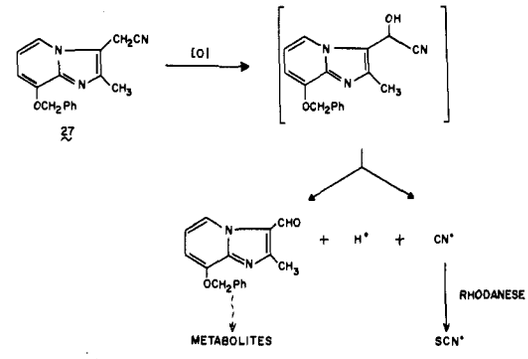


							antisecretory act.: % inhibn of acid secretion									
							histamine-stimulated dog									cytoprotective act.: EtOH ulcer, ED_{50}^{po}, mg/kg
							iv dose, mg/kg					oral dose, mg/kg				
no.	R_2	R_3	R	R′	Y	PL rat,[i] 40 mg/kg, ip	5	2	1	0.1	ED_{50}^{iv}, mg/kg	8	4	2	ED_{50}^{po}, mg/kg	
27	CH_3	CH_2CN	$PhCH_2O$	H	HC	98	99	95	83	49	0.09 (0.01–1.19)	77	42	20	4.4 (2.1–14.0)	3.0
30	CH_3	CH_3	$PhCH_2O$	5-CH_3	HC	26		13								8.0
31	CH_3	CH_3	$PhCH_2O$	6-CH_3	HC	86		45				71	0			8.2
32	CH_3	CH_3	$PhCH_2O$	H	CH_3C	92		70				35				16.0
33	CH_3	CH_2CN	$PhCH_2O$	5-CH_3	HC	*a*	0						11			8.0
34	CH_3	CH_2CN	$PhCH_2O$	H	CH_3C	99		90	74		0.53[b] (0.22–1.22)	59	20	8	7.8 (3.2–38.3)	13.0
39	CH_3	CH_2CN	$PhCH_2O$	H	HC, 5,6,7,8-H_4	44	0									
40	CH_3	NH_2	$PhCH_2O$	H	HC	99		97		55	0.10[c] (0.01–1.19)	96	74	50	2.0[f]	6.0
43	H	NH_2	$PhCH_2O$	H	HC	32		81	49			43				9.1
44	CH_3CH_2	NH_2	$PhCH_2O$	H	HC	83			72			59				5.2
45	*n*-C_3H_7	NH_2	$PhCH_2O$	H	HC	31		45				0				
46	*i*-C_3H_7	NH_2	$PhCH_2O$	H	HC	0		24				0				2.7
47	*n*-C_4H_9	NH_2	$PhCH_2O$	H	HC	26		45				0				7.5
48	*t*-C_4H_9	NH_2	$PhCH_2O$	H	HC	0	2					0				15.0
49	CH_3	NH_2	2-$FC_6H_4CH_2O$	H	HC	93		93				93	46	20		6.6
50	CH_3	NH_2	4-$FC_6H_4CH_2O$	H	HC	95		95				93	60	55		4.8
51	CH_3	NH_2	4-$ClC_6H_4CH_2O$	H	HC	66			74			92	81	32		2.2
52	CH_3	NH_2	4-$CF_3C_6H_4CH_2O$	H	HC	78		0				8				6.5
53	CH_3	NH_2	2-$PyCH_2O$	H	HC	16		24				15				2.3
54	CH_3	NH_2	2-thienyl-CH_2O	H	HC	70		77		12		86	80	30		5.0
55	CH_3	NH_2	3-thienyl-CH_2O	H	HC	52		82				88	86	29		8.4
56	CH_3	NH_2	$PhCH_2NH$	H	HC	84		98				89				9.6
57	CH_3	NH_2	$PhCH_2S$	H	HC	0		0				11				5.7
58	CH_3	NH_2	$PhCH_2CH_2O$	H	HC	56		39				39				5.2
59	CH_3	NH_2	PhO	H	HC	34		40				19				5.0
60	CH_3	NH_2	CH_2OPh	H	HC	27	34					39				6.6
61	CH_3	NH_2	$PhCH_2CH_2$	H	HC	47		71	46			52	41	19		9.0
62	CH_3	NH_2	H	H	$PhCH_2CH_2C$	50		17				0				5.2
63	CH_3	NH_2	H	6-$PhCH_2CH_2$	HC	52		6				0				5.7
64	CH_3	NH_2	H	5-$PhCH_2CH_2$	HC	40[a]										14.0
65	CH_3	NH_2	$PhCH_2O$	6-CH_3	HC	65		46				50				2.3
66	CH_3	NH_2	$PhCH_2O$	H	CH_3C	60		55				64	36			13.5
67	CH_3	NH_2	$PhCH_2O$	H	N	79		65	56		0.8[d] (0.2–6.0)	70	69	63	1.4[e] (0.6–3.9)	5.0
68	CH_3	NH_2	$PhCH_2CH_2$	H	N		18					15				
69	CH_3	CH_2NH_2	$PhCH_2O$	H	HC	46	49					9				5.5
70	CH_3	$CH_2CH_2NH_2$	$PhCH_2O$	H	HC	63		6				9				
71	CH_3	HCONH	$PhCH_2O$	H	HC	49		3								10.0
72	CH_3	CH_3CONH	$PhCH_2O$	H	HC	93		24				44				4.6
73	CH_3	CH_3CONH	$PhCH_2CH_2$	H	HC	40	3					16				12.0
74	CH_3	CH_3O_2CNH	$PhCH_2O$	H	HC	0										
75	CH_3	$PhCH_2O_2CNH$	$PhCH_2O$	H	HC	8		82					17			
76	CH_3	$(CH_3)_2NCHN$	$PhCH_2O$	H	HC	64		12				0				4.8
77	CH_3	$CH_3NHCONH$	$PhCH_2O$	H	HC	22	27					0				
78	CH_3	CH_3NH	$PhCH_2O$	H	HC	55[a]										9.8
79	CH_3	CH_3CH_2NH	$PhCH_2O$	H	HC	95	70	32				68				3.5
80	CH_3	CH_3CH_2NH	$PhCH_2CH_2$	H	HC	78	11					65				5.2
81	CH_3	*n*-C_3H_7NH	$PhCH_2O$	H	HC	99			12			68				5.3
82	CH_3	*i*-C_3H_7NH	$PhCH_2O$	H	HC	18	0									16.0

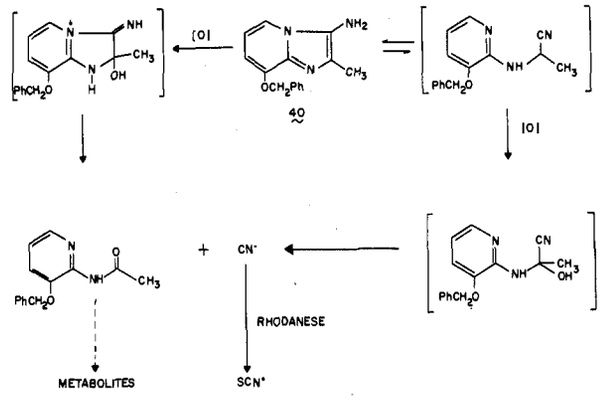
83	CH_3	$PhCH_2NH$	$PhCH_2O$	H	HC	48	0				2.5
84	CH_3	CH_3CH_2NH	$PhCH_2O$	H	N	48	0				6.0
85	CH_3	$(CH_3)_2N$	$PhCH_2O$	H	HC	76		35	72		2.8
86	CH_3	$(n\text{-}C_3H_7)_2N$	$PhCH_2O$	H	HC	60	0				8.4
87	CH_3	CH_3O	$PhCH_2O$	H	HC	49		37	0		3.6
88	CH_3	CH_3O	$PhCH_2CH_2$	H	HC	45		0			20.0
89	CH_3	CH_3S	$PhCH_2CH_2$	H	HC	28		0			8.5
90	CH_3	HO	$PhCH_2CH_2$	H	HC	32		0			9.6
91	CH_3	CH_3CO_2	$PhCH_2CH_2$	H	HC	64		6	0		inactive
cimetidine											inactive

[a] Lethalities observed in the pharmacologic evaluation of the test drug. [b] Determination of the intravenous ED_{50} included the percents inhibition of acid secretion at doses of 0.4 and 0.2 mg/kg, which were 39 and 1, respectively. [c] Determination of the intravenous ED_{50} included the percents inhibition of acid secretion at doses of 0.2 and 0.05 mg/kg, which were 41 and 15, respectively. [d] Determination of the intravenous ED_{50} included the percents inhibition of acid secretion at doses of 0.4 and 0.2 mg/kg, which were 41 and 15, respectively. [e] Determination of the oral ED_{50} included the percents inhibition of acid secretion at doses of 16 and 1 mg/kg, which were 92 and 39, respectively. [f] Estimated ED_{50}; regression was not significant at $\rho = 0.05$. [g] The intraperitoneal dose of cimetidine that produced a 50% inhibition of the 4-h acid output in the pylorus-ligated rat (ED_{50}) was 26.1 (12.8–50.9) mg/kg. [h] The intravenous dose of cimetidine required to reduce acid output to 50% of control value (ED_{50}) was 0.66 (0.16–2.60) mg/kg, while the oral dose (ED_{50}) was 1.25 (0.58–2.52) mg/kg. [i] PL = pylorus-ligated.

Scheme II. Proposed Metabolic Pathway of the 3-Cyanomethyl Function in 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**27**)



Scheme III. Proposed Metabolic Pathway(s) of the 3-Amino Function in 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**)



amount of radioactivity and correcting for the molecular weight difference.) Graphical analysis (Figures 4 and 5) of the data clearly shows that, for both routes of drug administration, the concentration–time profile of unchanged **27**, but not thiocyanate, closely resembles that of antisecretory activity. These observations suggest that unchanged **27** is the pharmacologically active species after the drug is administered and that its antisecretory activity is related, at least in part, to its secretion into the gastric lumen.

A metabolism study was also performed on the prototype compound 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**40**). Compound **40** labeled with ^{13}C and ^{14}C at the 3-position (compounds **41** and **42**, respectively) was given orally (40 mg/kg) to a single dog, and its urine was collected for 48 h after dosing. Thin-layer radiochromatography suggested three major metabolic fractions in urine. Fraction 1 (5.0% of urinary radioactivity) had an R_f identical with that of unchanged **40**. Fraction 2 (20.1% of urinary radioactivity) had an R_f identical with that of thiocyanate. Subsequent purification and mass spectral analysis confirmed that this fraction was thiocyanate. Fraction 3 (68.4% of urinary radioactivity) was a very polar compound, which was not characterized, although it was determined that it was not cyanide.

Interestingly, compound **40**, like **27**, is metabolized to cyanide. The cyanide produced is effectively detoxified in the liver to thiocyanate by the enzyme rhodanese. However, the mechanism of producing cyanide from **40** must be significantly different from that of generating cyanide from **27**. Proposed metabolic pathways are described in Scheme III.

The loss of the radioactive label, in both cases, inhibited determination of the metabolic fate of the imidazo[1,2-*a*]pyridine system. However, the principal metabolites of

Table VII. Plasma and Gastric Juice Concentrations of Radioactivity, Gastric Juice Levels of Thiocyanate and 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**), and Percent Inhibition of Gastric Acid Output in Dogs Dosed Intravenously with 3-([*cyano*-^{14}C]Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**29**) (0.2 mg/kg)

	mean concn ± SD, μg/mL				
time, h	radioact in plasma	radioact in gastric juice	SCN in gastric juice	**27** in gastric juice	% inhibn
0	0	0	0	0	0
0.5	0.13 ± 0.03	0.18 ± 0.11	0.02 ± 0.01	0.06 ± 0.04	62.7 ± 7.2
1.0	0.14 ± 0.04	1.61 ± 1.00	0.22[a]	1.29[a]	92.0 ± 8.0
1.5	ND[b]	2.09 ± 1.04	0.13 ± 0.12	1.60 ± 0.82	86.4 ± 18.1
2.0	0.14 ± 0.04	2.10 ± 0.66	0.22 ± 0.05	1.05 ± 0.87	71.6 ± 23.1
2.5	ND	1.64 ± 0.67	0.23 ± 0.06	0.53 ± 0.74	50.3 ± 24.5
3.0	0.12 ± 0.03	1.26 ± 0.74	0.24 ± 0.12	0.11 ± 0.16	32.2 ± 12.3
3.5	ND	1.10 ± 0.33	0.22 ± 0.06	0.03 ± 0.05	5.6 ± 4.7
4.0	0.10 ± 0.03	0.78 ± 0.26	0.16 ± 0.06	0	−7.9 ± 13.0

[a] Insufficient gastric juice produced by two dogs for determination of radioactivity and **27**. [b] ND = not determined.

Table VIII. Plasma and Gastric Juice Concentrations of Radioactivity, Gastric Juice Levels of Thiocyanate and 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**27**), and Percent Inhibition of Gastric Acid Output in a Single Dog Dosed Orally with 3-([*cyano*-^{14}C]Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo-[1,2-*a*]pyridine (**29**) (4 mg/kg)

	concn, μg/mL				
time, h	radioact in plasma	radioact in gastric juice	SCN in gastric juice	**27** in gastric juice	% inhibn
0	0	0	0	0	0
0.5	1.82	1.79	0.32	0.25	42.4
1.0	2.90	*a*	*a*	5.50	86.0
1.5	ND[b]	26.71	4.12	7.04	83.0
2.0	3.38	31.12	5.48	4.95	71.0
2.5	ND	35.74	6.93	2.65	36.1
3.0	3.08	33.40	6.93	0.30	0.0
3.5	ND	27.08	5.61	0.30	−39.2
4.0	3.14	25.20	5.21	0.30	−46.0

[a] Insufficient gastric juice produced for determination of **27**. [b] ND = not determined.

the antiulcer agent zolimidine (2-[4-(methylsulfonyl)-phenyl]imidazo[1,2-*a*]pyridine), isolable in human urine after oral administration of the drug, have been identified as the 5,6- and 7,8-dihydroxylated dihydro derivatives, respectively, as well as the bisglucuronidated adduct of the former compound.[19] On the assumption that ring hydroxylation analogous to that demonstrated to occur in the metabolism of zolimidine might be operative in our series, affecting metabolism of the pyridyl portion of the imidazo[1,2-*a*]pyridine ring system served as a working hypothesis for the design of a successor to prototype compound **27**.

In summary, the 3-cyanomethyl and 8-phenylmethoxy groups have been established as metabolic sites in **27**. The pyridyl portion of the imidazo[1,2-*a*]pyridine system has also been "proposed" as a site of metabolism on the basis of the reported metabolism of zolimidine. On the basis of these results, structure–activity studies directed toward discovery of a successor to **27** have focused on the identification of a bioequivalent for the 3-cyanomethyl function and/or structural alteration of the imidazo[1,2-*a*]pyridine system such as to warrant the expectation of a metabolic disposition different from that of **27**. The results of these studies are discussed in the following section.

Structure–Activity Relationships

The histamine stimulated dog data described in Table IV suggested the following structure–activity relationships.

3-Cyanomethyl Congeners. Modification of the Imidazo[1,2-*a*]pyridine System. The effect of introducing a methyl group in the 5-, 6-, or 7-position of the imidazo[1,2-*a*] pyridine system on gastric antisecretory activity was tested by examining the 3-methyl-substituted analogues **30**, **31**, and **32**, respectively. Only the 7-methyl-substituted analogue **32** exhibited significant intravenous antisecretory activity, but no antisecretory activity was observed following oral administration. In contrast, the corresponding 3-cyanomethyl-substituted analogue **34** exhibited both significant intravenous and oral antisecretory potency. However, the antisecretory and cytoprotective potency of **34** was somewhat reduced relative to **27**.

Structural alteration of the imidazo[1,2-*a*]pyridine system and its effect on gastric antisecretory activity were examined by testing the 5,6,7,8-tetrahydro analogue **39**. The lack of gastric antisecretory activity of **39** following intravenous administration illustrates the necessity for retaining the imidazo[1,2-*a*]pyridine system intact.

3-Amino Congeners. The gastric antisecretory and cytoprotective properties of a significant number of substituted imidazo[1,2-*a*]pyridines containing different functional groups at the 3-position have been described previously.[1] It became apparent after introduction of a considerable number of 3-substituents with widely varying physical and chemical properties that the cyanomethyl group was uniquely effective in imparting the desired levels of oral antisecretory activity combined with cytoprotective action.

We have recently discovered that the 3-amino substituent is a satisfactory, perhaps superior, surrogate for the cyanomethyl moiety. The discussion that follows summarizes the essential results of the structure–activity relationships of the 3-amino-substituted congeneric series.

R_3 Substituent. 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**) exhibited intravenous antisecretory potency in the dog comparable to that of **27**. Interestingly, the oral antisecretory potency of **40** in the dog, ED_{50} = 2.0 mg/kg (approximate), may be greater than that of **27**, ED_{50} = 4.4 (2.1–14.0) mg/kg. Introducing methylene groups between the 3-amino group and the imidazo[1,2-*a*]pyridine system produced analogues **69** and **70**. In both cases, their antisecretory activity was reduced relative to **40**.

Acylation of the 3-amino group with a variety of acylating agents produced analogues **71–77**. None of these N-acylated products exhibited antisecretory activity comparable to that of **40**.

The effect of alkylation of the 3-amino group on gastric antisecretory activity was examined by testing analogues **78–86**. Only 3-(ethylamino)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**79**) exhibited antisecretory and cytoprotective activity comparable to that of **40**.

Functional groups at the 3-position of the imidazo[1,2-*a*]pyridine system containing alternative heteroatoms (e.g., oxygen and sulfur) and their effect on gastric antisecretory

activity were examined by testing analogues 87–91. None of these compounds exhibited significant antisecretory activity.

R_2 Substituent. The presence of an alkyl group at the 2-position of the imidazo[1,2-*a*]pyridine system appeared to be necessary to maintain oral antisecretory potency. The 2-methyl-substituted analogue **40** was the most active, while the oral antisecretory activity of the 2-hydrogen-substituted analogue **43** was lower. Introduction at position 2 of straight- or branched-alkyl substituents larger than methyl resulted in a reduction of oral antisecretory activity relative to **40**.

R_8 Substituent. Substituted Phenyl. Introduction of an *o*-fluoro, *p*-fluoro, or *p*-chloro substituent into the 8-phenylmethoxy group of **40** produced analogues **49**, **50**, and **51**, respectively. The oral antisecretory activities of **49–51** in the dog were comparable to the activity of the unsubstituted-phenylmethoxy analogue **40**. Interestingly, introduction of an electron-withdrawing substituent into the 8-phenylmethoxy group of **40** which cannot mesomerically donate electrons leads to a less active analogue, **50** (Table VI).

Aromatic Replacement. Isosteric replacement of the 8-phenylmethoxy group in **40** with the 2-thienylmethoxy substituent or the 3-thienylmethoxy substituent gave analogues **54** and **55**, respectively. The oral antisecretory activity in the dog and the cytoprotective activity in the rat of **54** and **55** were comparable to the corresponding activities of **40**.

Replacement of the 8-phenylmethoxy substituent in **40** with the 2-pyridylmethoxy group produced analogue **53**. This substituted imidazo[1,2-*a*]pyridine exhibited reduced antisecretory activity relative to **40**.

Heteroatom Substitution. Substitution of the oxygen atom in the 8-phenylmethoxy substituent of **40** with a nitrogen atom resulted in the 8-(phenylmethyl)amino analogue **56**. The oral antisecretory activity in the dog and the oral cytoprotective activity in the rat of **56** were comparable to those of **40**.

On the other hand, substitution of the oxygen atom in the 8-phenylmethoxy substituent of **40** with a sulfur atom led to analogue **57**, which exhibited oral cytoprotective activity, but lacked both intravenous and oral antisecretory activity.

Homologation. The 8-phenylmethoxy substituent in **40** was homologated by increasing (analogue **58**) and decreasing (analogue **59**) the number of methylene groups between the oxygen atom and the phenyl ring. In both cases, reduced antisecretory activity relative to **40** was observed.

The effect of reversing the oxygen and methylene moieties of the 8-substituent was evaluated by comparing analogues **40** (8-phenylmethoxy) and **60** (8-phenoxymethyl). Although the oral cytoprotective activities of **40** and **60** were comparable, the antisecretory activity of **60** was significantly reduced relative to **40**.

Heteroatom Replacement. Replacement of the oxygen atom in the 8-phenylmethoxy substituent of **40** with a methylene group resulted in the 8-(2-phenylethyl) analogue **61**. While **61** exhibited both significant intravenous and oral antisecretory activity, its potency was somewhat reduced relative to **40**. Interestingly, the 7-(2-phenylethyl) (**62**), the 6-(2-phenylethyl) (**63**), and the 5-(2-phenylethyl) (**64**) isomers all exhibited oral cytoprotective activity in the rat comparable to that of **61**. However, neither **62**, **63**, nor **64** exhibited any significant antisecretory activity in the dog.

Modification of the Imidazo[1,2-*a*]pyridine System. The effect of introducing a methyl group in the imidazo-[1,2-*a*]pyridine system on gastric antisecretory activity was tested by examining the 6-methyl-substituted and 7-methyl-substituted analogues **65** and **66**, respectively. The antisecretory activity in the dog and the cytoprotective activity in the rat of **65** and **66** were comparable. However, relative to **40**, the antisecretory and cytoprotective activities of **65** and **66** were somewhat reduced. Interestingly, the antisecretory and cytoprotective potencies of **66** were comparable to those exhibited by the 7-methyl-3-cyanomethyl analogue **34**.

Structural alteration of the imidazo[1,2-*a*]pyridine system and its effect on gastric antisecretory activity were further examined by testing the imidazo[1,2-*a*]pyrazine congener **67**. 3-Amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyrazine (**67**) exhibited intravenous antisecretory potency in the dog comparable to that of **40** or **27**. Furthermore, the oral antisecretory potency of **67** in the dog, ED_{50} = 1.4 (0.6–3.9) mg/kg, may be greater than that of either **40**, ED_{50} = 2.0 mg/kg (approximate), or **27**, ED_{50} = 4.4 (2.1–14.0) mg/kg.

Replacement of the oxygen atom in the 8-phenylmethoxy substituent of **67** with a methylene group produced the 8-(2-phenylethyl) analogue **68**. Surprisingly, both the intravenous and oral antisecretory activities of **68** were substantially reduced relative to **67**. This result is in distinct contrast to the partial reduction in antisecretory activity that is observed when the identical isosteric substitution is made in **40** (compare the antisecretory activity of **40** and **61**).

In conclusion, on the basis of consideration of established and proposed metabolic sites of the imidazo[1,2-*a*]pyridine prototype **27** and a systematic alteration of key structural moieties at these sites, it has been possible to design analogues retaining both the antisecretory and cytoprotective properties. Furthermore, these analogues exhibit sufficient structural variation relative to the prototype **27** to warrant the expectation that they will be metabolized differently from **27**. Four compounds exhibiting the requisite profile have been identified, 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**34**), 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**40**), 3-amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**61**), and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**). One of these, 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyrazine (**67**), has been selected as a successor to the prototype 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, Sch 28080 (**27**).[31,32]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded by using a Varian CFT-20 spectrometer, IR spectra were recorded by using a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined by using a Varian MAT CH5. Microanalyses were performed by the Physical-Analytical Services Department of the Schering-Plough Corporation.

Chemistry. Preparation of Substituted 2-Aminopyridines and 2-Aminopyrazines (1). 2-Amino-4-methyl-3-(phenylmethoxy)pyridine (1b). Acetic anhydride (2 L) was heated under reflux, and the oil bath (140 °C) was removed. 4-Methyl-pyridine *N*-oxide, 1000 g (9.2 mol), was added in portions

(32) Chiu, P. J. S.; Barnett, A.; Tetzloff, G.; Kaminski, J. *Arch. Int. Pharmacodyn. Ther.* **1984**, *270*, 116.
(33) Chiu, P. J. S.; Barnett, A.; Gerhart, C.; Policelli, M.; Kaminski, J. *Arch. Int. Pharmacodyn. Ther.* **1984**, *270*, 128.

to maintain heating under reflux. After the addition was complete (1.5 h), the reaction mixture was removed under reduced pressure and the residue obtained was stirred with a saturated solution of sodium bicarbonate (2 L). The mixture was extracted with dichloromethane (4 × 600 mL). The dichloromethane extracts were combined and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure. Distillation in vacuo gave a yellow oil, 898 g (5.9 mol), 64%, bp 98–102 °C (0.15 mm), which was identified by proton magnetic resonance as a mixture of 4-(acetoxymethyl)pyridine (60%) and 4-methyl-3-acetoxypyridine (40%).[25] The mixture of acetates isolated was used without further purification.

To 384 g of potassium hydroxide (85%) dissolved in ethanol (2.5 L) was added a mixture of 4-(acetoxymethyl)pyridine (60%) and 4-methyl-3-acetoxy-pyridine (40%), 890 g (5.9 mol). The solution was stirred at room temperature overnight, and the ethanol was removed under reduced pressure. The residue obtained was dissolved in water (500 mL) and neutralized to pH 7 by the addition of concentrated hydrochloric acid. The neutral solution was extracted with dichloromethane (500 mL), a mixture of dichloromethane and ethyl acetate (800 mL, 3/5 by volume), and ethyl acetate (3 × 300 mL). The extracts were combined and dried ($MgSO_4$). Following filtration, the solvents were removed under reduced pressure. Distillation in vacuo gave a colorless oil, 478 g (4.4 mol), 74%, bp 128–132 °C (1.1 mm), which was identified by proton magnetic resonance as a mixture of 4-(hydroxymethyl)pyridine (70%) and 4-methyl-3-hydroxypyridine (30%). The mixture of hydroxylated pyridines isolated was used without further purification.

To 800 mL of concentrated sulfuric acid at 10 °C was added a mixture of 4-(hydroxymethyl)pyridine (70%) and 4-methyl-3-hydroxypyridine (30%), 138 g (1.3 mol), while the temperature of the reaction mixture was maintained below 30 °C. After the addition was complete (0.5 h), a cooled mixture of concentrated nitric acid (60 mL) and concentrated sulfuric acid (115 mL) was added, first at a rate for the reaction mixture to attain a temperature of 40 °C, and then the rate of addition was adjusted to maintain a reaction temperature between 40 and 45 °C. After the addition was complete (1.5 h), the reaction mixture was stirred at room temperature and poured into a mixture of ice and water (2 L) and the solution was adjusted to pH 1.5 by the addition of concentrated ammonium hydroxide. The solid that separated was isolated by filtration, washed thoroughly with water, and dried. Recrystallization from ether–hexane, 1/6 by volume, gave 45.2 g (0.29 mol), 74% (based on the amount of 4-methyl-3-hydroxypyridine in the mixture), of 2-nitro-3-hydroxy-4-methylpyridine, mp 83–85 °C.[26] The 2-nitro-3-hydroxy-4-methylpyridine isolated was used without further purification.

To 22 g (0.14 mol) of 2-nitro-3-hydroxy-4-methylpyridine dissolved in ethanol (750 mL) was added hydrazine hydrate (22 mL). The suspension that formed was heated to 65 °C, and Raney nickel (5 g) was added cautiously in 1-g portions to the well-stirred mixture. After 0.5 h, an additional 10 mL of hydrazine hydrate was added followed by Raney nickel (5 g), added in 1-g portions. The mixture was stirred for 2 h at room temperature, and the Raney nickel catalyst was removed by filtration. The filtrate was decolorized with charcoal and filtered, and the volatiles were removed under reduced pressure. Recrystallization from ethyl acetate gave 13.2 g (0.11 mol), 79%, of 2-amino-3-hydroxy-4-methylpyridine, mp 175–177 °C dec. The 2-amino-3-hydroxy-4-methylpyridine isolated was used without further purification.

Via the procedure described by Bristol et al.,[28] phase-transfer alkylation of 2-amino-3-hydroxy-4-methylpyridine with benzyl chloride gave 2-amino-3-(phenylmethoxy)-4-methylpyridine (**1b**), Table I.

2-Amino-3-(phenylmethoxy)-5-methylpyridine (**1c**) and 2-amino-3-(phenylmethoxy)-6-methylpyridine (**1d**), Table I, were prepared from 5-methyl-3-hydroxypyridine and 6-methyl-3-hydroxypyridine, respectively, by following the methods[26,27,28] described for the preparation of 2-amino-3-(phenylmethoxy)-4-methylpyridine (**1b**).

2-Amino-3-(phenylmethoxy)pyrazine (1k). To 1.65 g (0.069 mol) of sodium hydride (60%) in mineral oil suspended in 20 mL of *N,N*-dimethylformamide was added 4.65 g (0.04 mol) of benzyl alcohol, and the mixture was stirred at ambient temperature for 1 h under a nitrogen atmosphere. 2-Amino-3-chloropyrazine (**1j**), 5.05 g (0.04 mol), dissolved in 50 mL of *N,N*-dimethylformamide was added rapidly, and the mixture was heated at 100 °C for 1.5 h. Upon cooling to room temperature, the volatiles were removed in vacuo, 50 °C (0.7 mm), and the residue obtained was dissolved in dichloromethane (150 mL). The dichloromethane solution was washed with water (4 × 20 mL) and brine (50 mL) and dried ($MgSO_4$). Following filtration, the dichloromethane was removed under reduced pressure to give a mixture of a solid and an oil, 8.9 g. Drying on a porcelain plate gave 4.82 g (0.024 mol), 60%, of 2-amino-3-(phenylmethoxy)pyrazine (**1k**), mp 68–74 °C. Anal. ($C_{11}H_{11}N_3O \cdot {}^1/_2H_2O$) C, H, N.

Preparation of Substituted Imidazo[1,2-*a*]pyridines and Imidazo[1,2-*a*]pyrazines. Method A. 2,7-Dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (3). A mixture of 2.15 g (0.01 mol) of 2-amino-3-(phenylmethoxy)-4-methylpyridine (**1b**) and 1.2 g (0.013 mol) of chloroacetone (**2b**) in 30 mL of methanol was heated under reflux for 24 h. The methanol was removed under reduced pressure to give a brown oil. Treatment with ether gave a solid, which was isolated by filtration, 2.6 g. Recrystallization from methanol–ether gave 2.5 g (0.0086 mol), 86%, of 2,7-dimethyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine hydrochloride (**3**), mp 151–154 °C. Anal. ($C_{16}H_{16}N_2O \cdot HCl$ C, H, N, Cl.

The substituted imidazo[1,2-*a*]pyridines and -pyrazines **4–8**, **30–34**, and **87–89** (Table III) were prepared by using the procedure described above, method A.

Method B. 2-Methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]pyridine (12). To a stirred suspension of 25.8 g (0.17 mol) of 8-hydroxy-2-methylimidazo[1,2-*a*]pyridine (**11**) in 200 mL of *N,N*-dimethylformamide at 0–5 °C under nitrogen was added 7.7 g (0.32 mol) of sodium hydride (60%) in mineral oil. After the mixture was stirred at 0 °C for 0.5 h, 30.1 g (0.17 mol) of 3-thenyl bromide[10] was added and the mixture was heated at 70 °C for 3 h. The volatiles were removed in vacuo and the residue obtained partitioned between water (100 mL) and chloroform (300 mL). The chloroform layer was separated, washed with water (100 mL), and dried ($MgSO_4$). Following filtration, the chloroform was removed under reduced pressure to give an oil. The residual oil was dissolved in chloroform (50 mL) and passed through silica gel (20 g, 60H). Removal of the chloroform under reduced pressure gave a solid. Recrystallization from ethyl acetate gave 21.6 g (0.089 mol), 52%, of 2-methyl-8-(3-thienylmethoxy)imidazo[1,2-*a*]-pyridine (**12**), mp 134–135 °C. Anal. ($C_{13}H_{12}N_2OS$) C, H, N.

Method C. 3-Amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine Hydrochloride (40). Sodium bisulfite, 4.16 g (0.04 mol), was dissolved in distilled water (80 mL), and acetaldehyde (4 mL) was added. The mixture was stirred at room temperature for 0.5 h, and 8.0 g (0.04 mol) of 2-amino-3-(phenylmethoxy)pyridine (**1a**) was added. The mixture was heated to 90 °C, and sufficient *p*-dioxane (30 mL) was added to obtain a clear solution. The reaction mixture was heated at 90 °C for 1.5 h, and 1.96 g (0.05 mol) of sodium cyanide dissolved in distilled water (30 mL) was added. The mixture was heated under reflux overnight. After 18 h, *p*-dioxane (40 mL) was added followed by 3 M sodium hydroxide (30 mL), and the mixture was allowed to cool for 0.25 h before it was poured into water (500 mL). The mixture was extracted by using ethyl acetate (2 × 300 mL), and the extracts were combined, washed with water (300 mL), and dried (Na_2SO_4). Following filtration, the ethyl acetate was removed under reduced pressure. The residue obtained was chromatographed on silica gel (300 g, TLC grade). 2-Amino-3-(phenylmethoxy)pyridine (**1a**) was eluted by using chloroform, followed by elution of 3-amino-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (**40**) by using ethyl acetate. The fractions containing the desired product were combined, and the solvent was removed under reduced pressure to give an oil, which solidified on standing. The solid was dissolved in methanol (100 mL) and treated with 10 mL of ethereal hydrogen chloride (3 M). The solvent was removed under reduced pressure to give a solid. Recrystallization from ethanol–ethyl acetate gave 3.2 g (0.011 mol), 28%, of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine hydrochloride (**40**), mp 205–206 °C. Anal. ($C_{15}H_{15}N_3O \cdot HCl$) C, H, N, Cl.

The substituted imidazo[1,2-*a*]pyridines and -pyrazines **44–48**, **61**, **62**, **64**, and **67** (Table III) were prepared by using the procedure described above, method C.

Method D. 3-Amino-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (43). To 17.8 g (0.08 mol) of 8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**13**) dissolved in 400 mL of tetrahydrofuran was added dropwise with stirring 33.0 g (0.32 mol) of *n*-butyl nitrite. When the addition was complete, the solution was heated under reflux for 6 h. Upon cooling, the volatiles were removed under reduced pressure at 55 °C to give a green solid. Recrystallization from acetonitrile gave 14.5 g (0.06 mol), 75% of 3-nitroso-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, mp 168–171 °C, which was used without further purification.

3-Nitroso-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine, 10.0 g (0.04 mol), was dissolved in glacial acetic acid (220 mL) and water (110 mL) and the solution stirred at 0 °C. Powdered zinc, 12.9 g (0.2 mol), was added in portions while the temperature of the reaction mixture was maintained between 0 and 5 °C. When the addition was complete, the suspension was stirred at 0 °C for an additional 1 h. The volatiles were removed in vacuo at 25–30 °C. The residue obtained was dissolved in water (1.5 L) and basified by the addition of sodium hydroxide (3 M). The basic aqueous solution was extracted with dichloromethane (4 × 250 mL). The dichloromethane extracts were combined and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a brown oil, 1.7 g. The oil was dissolved in methanol and treated with 10 mL of ethereal hydrogen chloride (3 M). Recrystallization from methanol–ethyl acetate gave 1.4 g (0.005 mol), 12%, of 3-amino-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (**43**), mp 209–210 °C. Anal. ($C_{14}H_{13}N_3O$·HCl) C, H, N.

The substituted imidazo[1,2-*a*]pyridines **49–55**, **58**, and **60** (Table III) were prepared by using the procedure described above, method D.

Method E. 3-Amino-2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (56). To 1.25 g (0.005 mol) of 2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (**5**) dissolved in tetrahydrofuran (50 mL) was added dropwise with stirring 15 mL of *n*-butyl nitrite. When the addition was complete, the solution was heated under reflux for 0.75 h. Upon cooling to ambient temperature, ethanol (50 mL) was added and the solution was concentrated in vacuo to approximately 50 mL. The solution remaining was poured into 70 mL of concentrated hydrochloric acid containing stannous chloride monohydrate (10 g) heated to 60 °C. After stirring at ambient temperature for 1.5 h, the solution was poured onto ice (500 g) and 50% sodium hydroxide (100 g) was added with cooling. The solution was extracted with chloroform (2 × 300 mL). The chloroform extracts were combined and filtered through Celite. The chloroform was removed from the filtrate under reduced pressure to give an oil. Chromatography on silica gel eluting with ethyl acetate–chloroform gave a solid. Recrystallization from ethyl acetate–hexanes gave 0.32 g (0.001 mol), 24%, of 3-amino-2-methyl-8-[(phenylmethyl)amino]imidazo[1,2-*a*]pyridine (**56**), mp 145–155 °C. Anal. ($C_{15}H_{16}N_4$) C, H, N.

Method F. 3-Amino-2-methyl-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine (57). 2-Methyl-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine (**24**), 9.6 g (0.04 mol), was dissolved in glacial acetic acid (75 mL) and water (100 mL), and the solution was stirred at −15 °C. Sodium nitrite, 2.8 g (0.04 mol), dissolved in 40 mL of water was added dropwise. When the addition was complete, the suspension was stirred at −15 °C for 0.25 h and at ambient temperature for 3 h. The green solid that formed was isolated by filtration, thoroughly washed with water, and dried. There was obtained 8.5 g (0.032 mol), 80% of 2-methyl-3-nitroso-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine, mp 154–155 °C dec, which was used without further purification. 2-Methyl-3-nitroso-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine, 8.5 g (0.032 mol), was dissolved in glacial acetic acid (50 mL) and water (70 mL) and the solution stirred at 0 °C. Powdered zinc, 6.0 g (0.09 mol), was added in portions while the temperature of the reaction mixture was maintained at 0 °C. When the addition was complete, the suspension was stirred at ambient temperature for 1.25 h. The reaction mixture was filtered through glass wool and basified by the addition of concentrated ammonium hydroxide. The solid that formed was isolated by filtration and dissolved in ethyl acetate (300 mL). The ethyl acetate solution was washed with water (2 × 50 mL) and dried ($MgSO_4$). Following filtration, the ethyl acetate was removed under reduced pressure to give an oil. Chromatography on silica gel (300 g) eluting with 3% methanol in chloroform gave a solid, 4.4 g. Recrystallization from ethyl acetate–ether gave 3.5 g (0.013 mol), 41%, of 3-amino-2-methyl-8-[(phenylmethyl)thio]imidazo[1,2-*a*]pyridine (**57**), mp 132–134 °C. Anal. ($C_{15}H_{15}N_3S$) C, H, N, S.

The substituted imidazo[1,2-*a*]pyridines and -pyrazines **65–67** (Table III) were prepared by using the procedure described above, method F.

Method G. 3-Formamido-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (71). 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**), 8.9 g (0.035 mol), was dissolved in ethyl formate (90 mL), and the solution was heated under reflux for 24 h. The reaction mixture was cooled to 0 °C, and the solid that formed was isolated by filtration. Recrystallization from methanol–ethyl acetate gave 4.2 g (0.015 mol), 42%, of 3-formamido-2-methyl-(8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**71**), mp 191–192 °C. Anal. ($C_{16}H_{15}N_3O_2$) C, H, N.

Via the procedure described above, method G, acylation of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**) and 3-amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**61**) with the appropriate acylating reagent gave the corresponding substituted imidazo[1,2-*a*]pyridines **72–77**.

Method H. 2-Methyl-3-(methylamino)-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (78). 3-Formamido-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**71**) in 30 mL of anhydrous tetrahydrofuran at 0 °C was added dropwise, over 0.25 h, to 25 mL of borane in tetrahydrofuran (1 M), while the temperature was maintained between 0 and 5 °C. When the addition was complete, the reaction mixture was stirred at ambient temperature for an additional 20 h. The excess borane was decomposed at −20 °C by the addition of 6.5 mL of hydrochloric acid (6 M), and the volatiles were removed under reduced pressure. The residue obtained was dissolved in water and basified by the addition of sodium hydroxide (5 M). The basic aqueous solution was extracted with dichloromethane (3 × 200 mL). The dichloromethane extracts were combined and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give a solid, 2.1 g. Chromatography on silica gel eluting with chloroform–ethanol–concentrated ammonium hydroxide, 90/2/0.5 by volume, gave a solid, 1.9 g. The solid was dissolved in acetonitrile and treated with 10 mL of ethereal hydrogen chloride (3 M). The solid that formed was isolated by filtration, thoroughly washed with ether, and dried to give 1.8 g (0.006 mol), 76%, of 2-methyl-3-(methylamino)-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (**78**), mp 193.5–194 °C. Anal. ($C_{16}H_{17}N_3O$·HCl) C, H, N.

Via the procedure described above, method H, borane reduction of 3-acetamido-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**72**) and 3-acetamido-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**73**) gave the corresponding substituted imidazo[1,2-*a*]pyridines **79** and **80**.

Method I. 2-Methyl-8-(phenylmethoxy)-3-(*n*-propylamino)imidazo[1,2-*a*]pyridine Hydrochloride (81). A mixture of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**), 5.0 g (0.017 mol), propionaldehyde, 1.0 g (0.018 mol), and 3A molecular sieves (3 g) in 100 mL of methanol was stirred at ambient temperature for 1.5 h. The mixture was cooled to 0 °C, and 1.1 g (0.017 mol) of sodium cyanoborohydride was added in portions, with the temperature maintained between 0 and 5 °C. When the addition was complete, the reaction mixture was stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure, and the residue obtained was partitioned between water (60 mL) and dichloromethane (150 mL). The dichloromethane layer was separated and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give an oil, 5 g. Chromatography on silica gel eluting with ethyl acetate–petroleum ether, 1/1 by volume, gave an oil, 3.8 g. The oil was dissolved in methanol and treated with 10 mL of ethereal hydrogen chloride (3 M). The solvent was removed under reduced pressure to give a solid. Recrystallization from methanol–ethyl acetate gave 2.6 g (0.008 mol), 48%, of 2-methyl-8-(phenylmethoxy)-3-(*n*-propylamino)imidazo[1,2-*a*]pyridine hydrochloride (**81**), mp 153–155 °C. Anal. ($C_{18}H_{21}N_3O$·HCl) C, H, N, Cl. The substituted imidazo[1,2-*a*]pyridines **82–86** (Table III) were prepared by using the procedure described above, method I.

8-(Hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine (9). To a stirred suspension of 57.6 g (0.36 mol) of 8-formyl-2-methylimidazo[1,2-*a*]pyridine (8) in 400 mL of 2-propanol at 0 °C was added in portions 8.0 g (0.21 mol) of sodium borohydride. The reaction mixture was stirred at room temperature for an additional 2 h. The excess sodium borohydride was decomposed by the addition of distilled water and the solution concentrated under reduced pressure at 50 °C. The residue obtained was dissolved in water and extracted with chloroform. The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Recrystallization from dimethoxyethane gave 53.5 g (0.33 mol), 93%, of 8-(hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine (9), mp 132–137 °C. Anal. ($C_9H_{10}N_2O$) C, H, N.

2-Methyl-8-(phenoxymethyl)imidazo[1,2-*a*]pyridine (10). 8-(Hydroxymethyl)-2-methylimidazo[1,2-*a*]pyridine (9), 21.1 g (0.13 mol), was dissolved in 400 mL of dichloromethane. To the solution at 0 °C was added dropwise with stirring 19 mL of thionyl chloride. The reaction mixture was stirred for 1 h, and the dichloromethane was removed under reduced pressure to give 8-(chloromethyl)-2-methylimidazo[1,2-*a*]pyridine, TLC (silica gel, ethyl acetate–ethanol, 9/1 by volume) R_f 0.70, which was used without further purification.

To a stirred suspension of 0.62 g (0.026 mol) of sodium hydride in mineral oil (50%) in 60 mL of *N,N*-dimethylformamide was added 2.4 g (0.026 mol) of phenol in small portions at 5–10 °C, and the mixture was stirred for an additional 0.5 h at room temperature. The mixture was cooled to 5 °C, and a solution of 4.7 g (0.026 mol) of 8-(chloromethyl)-2-methylimidazo[1,2-*a*]-pyridine in 35 mL of *N,N*-dimethylformamide was added dropwise over 0.5 h, followed by 12 h at room temperature. The solvent was removed under reduced pressure, the residue partitioned between chloroform and water, and the aqueous layer extracted with chloroform. The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give a solid. Recrystallization from ether–hexanes gave 2.0 g (0.008 mol), 30%, of 2-methyl-8-(phenoxymethyl)imidazo[1,2-*a*]pyridine (10), mp 65–67 °C. Anal. ($C_{15}H_{14}N_2O$) C, H, N.

3-([*cyano*-^{13}C]Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (28). A mixture of 3.85 g (0.009 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)-methyl]imidazo[1,2-*a*]pyridine iodide (26) and 0.5 g (0.01 mol) of [^{13}C]sodium cyanide (90%) in 20 mL of *N,N*-dimethylformamide was heated at 80–100 °C for 2 h with stirring. The solid that formed was isolated by filtration, washed with water, and dried, 2.1 g. Recrystallization from ethyl acetate–ether gave 1.85 g (0.007 mol), 74% of 3-([*cyano*-^{13}C]cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (28), mp 161–162 °C. The percent ^{13}C enrichment was 86% determined by mass spectral analysis relative to the natural abundance of a reference sample (27).

3-([*cyano*-^{14}C]Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (29). Via the procedure described for the preparation of 28, but with [^{14}C]sodium cyanide, there was obtained 3-([*cyano*-^{14}C]cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (29), TLC (silica gel, acetone) R_f 0.77, 99.5% radiochemical purity, specific activity 28.4 μCi/mg.

8-Hydroxy-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]-pyridine Hydrochloride (35). A mixture of 5.9 g (0.025 mol) of 2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (14), 4.2 mL of hydrochloric acid (6 N), and 5.9 g of palladium on charcoal (10%) in 240 mL of ethanol was hydrogenated under a hydrogen pressure of 55 psi for 22 h at room temperature. An additional 2 g of palladium on charcoal (10%) was added and the hydrogenation continued for another 48 h. The catalyst was removed by filtration and thoroughly washed with ethanol, and the volatiles were removed under reduced pressure to give a solid. After drying, there was obtained 4.7 g (0.025 mol), 100% of 8-hydroxy-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine hydrochloride (35), mp 140–152 °C, which was used without further purification.

2-Methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine (36). To a stirred suspension of 3.0 g (0.02 mol) of 8-hydroxy-2-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (35) in 50 mL of *N,N*-dimethylformamide at 0–5 °C under nitrogen was added 1.02 g (0.04 mol) of sodium hydride in mineral oil (50%). After the mixture was stirred at 0 °C for 0.5 h, 2.5 g (0.02 mol) of benzyl chloride was added and the mixture heated at 85–90 °C for 1.5 h. The volatiles were removed under reduced pressure, and the residue obtained was dissolved in water (150 mL). The aqueous solution was extracted with a mixture of dichloromethane–ether, 1/1 by volume (3 × 150 mL). The extracts were combined and dried (Na_2SO_4). Following filtration, the solvents were removed under reduced pressure to give an oil. Chromatography on silica gel eluting with acetone–dichloromethane, 1/1 by volume, gave 2.4 g (0.01 mol), 52% of 2-methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]-pyridine (36) as a yellow oil, which was used without further purification: ^{1}H NMR (DMSO-d_6) δ 7.3 (s, 5 H), 6.7 (s, 1 H), 4.7 (s, 2 H), 4.4 (br t, 1 H), 3.6–4.1 (m, 2 H), 1.7–2.2 (m, 4 H), and 2.1 (s, 3 H).

3-[(Dimethylamino)methyl]-2-methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (37). A mixture of 3.0 g (0.012 mmol) of 2-methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (36), 1.2 g (0.014 mol) of dimethylamine hydrochloride, and 0.42 g (0.014 mol) of paraformaldehyde in 20 mL of ethanol was heated under reflux for 4 h. Upon cooling to ambient temperature, the volatiles were removed under reduced pressure. The residue obtained was dissolved in chloroform. The chloroform solution was washed with 5% potassium carbonate and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give an oil. Chromatography on silica gel eluting with acetone gave 3.0 g (0.01 mmol), 78%, of 3-[(dimethylamino)methyl-2-methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (37), mp 68–70 °C. Anal. ($C_{18}H_{25}N_3O$) C, H, N.

2-Methyl-8-(phenylmethoxy)-3-[(trimethylammonio)-methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine Iodide (38). To 2.6 g (0.009 mol) of 3-[(dimethylamino)methyl]-2-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (37) dissolved in 40 mL of acetone was added dropwise with stirring 1.4 g (0.01 mol) of methyl iodide. The solution was stirred for 16 h at room temperature. The volatiles were removed under reduced pressure to give 2.6 g (0.006 mol), 72% of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (39). A mixture of 3.5 g (0.006 mol) of 2-methyl-8-(phenylmethoxy)-3-[(trimethylammonio)methyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine iodide (38) and 1.2 g (0.02) of sodium cyanide in 30 mL of *N,N*-dimethylformamide was heated at 90 °C for 1.5 h with stirring. The solvent was removed in vacuo, and the residue obtained was partitioned between water (25 mL) and chloroform (50 mL). The layers were separated, and the aqueous layer was extracted with chloroform (3 × 50 mL). The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give an oil. Chromatography on silica gel eluting with acetone–dichloromethane, 1/1 by volume, gave 0.34 g (0.0012 mol), 20%, of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (39), mp 131.5–134.5 °C. Anal. ($C_{17}H_{19}N_3O \cdot 0.3H_2O$) C, H, N.

[3-^{13}C]-3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (41). Via the procedure described for the preparation of 40, method C, but with [^{13}C]sodium cyanide (90%), there was obtained 3.2 g (0.011 mol), 28%, of [3-^{13}C]-3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (41), mp 205–206 °C. The percent ^{13}C enrichment was 93% determined by mass spectral analysis relative to the natural abundance of a reference sample of 40.

[3-^{14}C]-3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Hydrochloride (42). Via the procedure described for the preparation of 40, method C, but with [^{14}C]sodium cyanide, there was obtained [3-^{14}C]-3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (42), TLC (silica gel, ethyl acetate) R_f 0.24, 98% radiochemical purity, specific activity 26.1 μCi/mg.

3-Amino-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]-pyrazine Hydrochloride (68). A solution of 5.7 g (0.03 mol) of phenethyl bromide in 15 mL of anhydrous ether was added dropwise with stirring to 0.8 g (0.03 mol) of magnesium in 15 mL of anhydrous ether. The suspension was heated under reflux for 2 h. Upon cooling to room temperature, the solution of phenethylmagnesium bromide, 6.5 g (0.03 mol), was added dropwise

to 4.0 g (0.02 mol) of 8-chloro-2-methylimidazo[1,2-*a*]pyrazine (**6**) and 40.0 mg (0.07 mmol) of lithium [1,3-bis(diphenylphosphino)propane]nickel(II) chloride dissolved in 75 mL of anhydrous tetrahydrofuran at 0 °C. When the addition was complete, the reaction mixture was stirred at ambient temperature for 16 h. Phosphoric acid (19%) in methanol was added, and the volatiles were removed under reduced pressure. The residue obtained was dissolved in water, basified with sodium carbonate to pH 8, and extracted with dichloromethane. The dichloromethane extracts were combined and dried (Na_2SO_4). Following filtration, the dichloromethane was removed under reduced pressure to give an oil, 4.9 g. The oil was dissolved in anhydrous ether and filtered through Celite. The ether was removed under reduced pressure to give 2.8 g (0.012 mol), 62%, of 2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyrazine, mp 50–52 °C, which was used without further purification.

Via the procedure described in method E, 2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyrazine was used to prepare 1.2 g (0.004 mol), 32%, of 3-amino-2-methyl-8-(2-phenylethyl)-imidazo[1,2-*a*]pyrazine hydrochloride (**68**), mp >250 °C. Anal. ($C_{15}H_{16}N_4$·HCl) C, H, N, Cl.

3-(Aminoethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine Dihydrochloride (70). To a stirred suspension of 2.0 g (0.007 mol) of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) in 25 mL of anhydrous tetrahydrofuran at ambient temperature was added dropwise, over 0.25 h, 16 mL of borane in tetrahydrofuran (1 M). When the addition was complete, the reaction mixture was stirred at ambient temperature for an additional 16 h. The excess borane was decomposed at −10 °C by the addition of 5 mL of hydrochloric acid (6 M), and the volatiles were removed under reduced pressure. The residue obtained was dissolved in water and basified by the addition of 25 mL of sodium hydroxide (5 M). The basic aqueous solution was extracted with chloroform (3 × 150 mL). The chloroform extracts were combined and dried (Na_2SO_4). Following filtration, the chloroform was removed under reduced pressure to give an oil. The oil was dissolved in a mixture of methanol (2 mL) and dichloromethane (23 mL) and treated with 5 mL of ethereal hydrogen chloride (4 M). The solid that formed was isolated by filtration, thoroughly washed with ether, and dried. Recrystallization from methanol–ethyl acetate gave 0.7 g (0.002 mol), 35%, of 3-(aminoethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine dihydrochloride (**70**), mp 164 °C dec. Anal. ($C_{17}H_{19}N_3O$·2HCl) C, H, N, Cl.

3-Hydroxy-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]-pyridine Hydrobromide (90). To 2.7 g (0.011 mol) of boron tribromide in dichloromethane (100 mL) at −6 °C was added dropwise with stirring 3.5 g (0.01 mol) of 3-methoxy-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]pyridine (**88**) dissolved in dichloromethane (70 mL). The reaction temperature was maintained at −60 °C throughout the addition. When the addition was complete, the reaction was stirred at ambient temperature for 24 h. Addition of water (3 mL) and ether (35 mL) gave a suspension. The solid that formed was isolated by filtration and triturated with a mixture of acetone (335 mL) and ether (335 mL). Recrystallization from methanol–ethyl acetate gave 2.0 g (0.006 mol), 59%, of 3-hydroxy-2-methyl-8-(2-phenylethyl)imidazo-[1,2-*a*]pyridine hydrobromide (**90**), mp 229–231 °C dec. Anal. ($C_{16}H_{16}N_2O$·HBr) C, H, N, Br.

3-Acetoxy-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]-pyridine Hydrochloride (91). To a suspension of 1.3 g (0.004 mol) of 3-hydroxy-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]-pyridine (**90**) in acetone (14 mL) were added 0.7 g (0.006 mol) of acetic anhydride and 1.3 g (0.013 mol) of triethylamine. The reaction mixture was stirred at ambient temperature for 5 h. The reaction mixture was partitioned between water and a dichloromethane–ether mixture. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 150 mL). The extracts were combined and dried (Na_2SO_4). Following filtration, the solvents were removed under reduced pressure to give an oil. Chromatography on silica gel eluting with ethyl acetate–petroleum ether, 1/1 by volume, gave a solid, 0.9 g. The solid was dissolved in ether and treated with 4 mL of ethereal hydrogen chloride (3.4 M). The solid that formed was isolated by filtration, thoroughly washed with ether, and dried. Recrystallization from methanol–isopropyl ether gave 0.7 g (0.002 mmol), 40%, of 3-acetoxy-2-methyl-8-(2-phenylethyl)imidazo[1,2-*a*]-pyridine hydrochloride (**91**), which exhibited a broad composition range beginning at approximately 140 °C. Anal. ($C_{18}H_{18}N_2O_2$·HCl·0.4H_2O) C, H, N, Cl.

Single Crystal X-ray Analysis of 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (67) as Its Hemimaleate (67)·Mal) and 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (40) as Its Hydrochloride (40)·HCl). Crystal Data. $C_{18}H_{18}N_4O_5$ (**67**·Mal): M_r 370.37, triclinic, a = 10.993 (2) Å, b = 12.214 (2) Å, c = 6.881 (1) Å, α = 101.98 (1)°, β = 100.23 (1)°, γ = 83.39 (1)°, V = 886.5 Å^3, Z = 2, d_{calcd} = 1.387 g cm^{-3}, μ(Cu Kα radiation, γ = 1.5418 Å) = 8.2 cm^{-1}. Space group $P1$ (C_1^1) or $P\bar{1}$ (C_i^1) from Laue symmetry; shown to be the latter by structure solution and refinement. Sample dimensions: 0.10 × 0.16 × 0.60 mm.

$C_{15}H_{16}ClN_3O$ (**40**·HCl): M_r 289.77, monoclinic, a = 9.651 (2) Å, b = 12.210 (1) Å, c = 13.896 (3) Å, β = 119.97 (1)°, V = 1418.5 Å^3, Z = 4, d_{calcd} = 1.357 g cm^{-3}, μ(Cu Kα radiation) = 23.9 cm^{-1}. Space group $P2_1/c$ (C_{2h}) uniquely defined by the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.04 × 0.30 × 0.40 mm.

Crystallographic Measurements. Preliminary unit-cell parameters and space group information were obtained from oscillation, Weissenberg, and precession photographs. Intensity data ($h, \pm k, \pm l$ for **67**·Mal; $h, k, \pm l$ for **40**·HCl) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, incident-beam graphite monochromator; ω–2θ scans, θ_{max} = 67°). From totals of 3158 (**67**·Mal) and 2381 (**40**·HCl) unique reflections after averaging equivalent forms, those 2522 and 1965, respectively, with $I > 3.0\sigma(I)$ were retained for the structure analyses and corrected for the usual Lorentz and polarization effects. Absorption corrections were not necessary for **67**·Mal, but empirical absorption corrections were applied to the data for **40**·HCl. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 reflections ($55° < \theta < 66°$ for **67**·Mal; $45° < \theta < 67°$ for **40**·HCl) widely separated in reciprocal space.

Structure Analyses. Both crystal structures were solved by direct methods.[29a] Approximate coordinates for non-hydrogen atoms were obtained from E maps. Difference Fourier syntheses evaluated following several cycles of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic thermal parameters yielded positions for all hydrogen atoms. Continuation of the least-squares refinement, with hydrogen atom positional and isotropic thermal parameters included as variables, led to convergence at R = 0.038 (R_w = 0.053)[30] for **67**·Mal and R = 0.42 (R_w = 0.060)[30] for **40**·HCl. Final positional and thermal parameters are listed in supplementary Tables I–III.[29b] Neutral atom scattering factors used in the structure-factor calculations were taken from ref 31. In the least-squares iterations, $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$; $\Delta = ||F_o| - |F_c||$] was minimized.

Determination of the pK_a of 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (27), 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (40) and 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (67). Duplicate titrations were performed potentiometrically on 0.0025% aqueous sample solutions of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) by using 0.001 N aqueous sodium hydroxide as the titrant, a Fisher pH electrode, and a Mettler automatic titrator. Similar titrations were performed, in triplicate, on a 0.0067%, 0.017%, and 0.025% aqueous sample solution of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (**40**) and 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**) by using 0.01 N aqueous sodium hydroxide as the titrant.

A plot of pH versus volume of sodium hydroxide solution was obtained, and the pK_a value of the sample was determined graphically for each of the above titrations.

The average pK_a of 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**27**) was 5.5, the average pK_a of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine hydrochloride (**40**) was 5.8, and the average pK_a of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyrazine (**67**) was 4.6.

Pharmacology. The compounds were evaluated for gastric antisecretory activity in the rat and dog and gastric cytoprotective activity in the rat by using the protocol that has been described

previously.[1] Six rats were used for each test compound and eight rats for the control. The intraperitoneal dose of cimetidine that produced a 50% inhibition of the 4-h acid output in the pylorus-ligated rat (ED_{50}) was 26.1 (12.8–50.9) mg/kg.[4] Unless otherwise noted in Table VI, each compound was tested in a single dog. Each animal served as its own control because the response to a set dose of histamine depends upon the size of the pouch and the pouch size is not constant across animals. In the Heidenhain pouch dog, the intravenous dose of cimetidine required to reduce acid output to 50% of control value (ED_{50}) was 0.66 (0.16–2.60) mg/kg, while the oral dose (ED_{50}) was 1.25 (0.58–2.52) mg/kg. The estimated oral ED_{50} values for carbenoxolone and PGE_2 against ethanol-induced lesions in rats were 30 and <0.1 mg/kg, respectively.[4]

Drug Metabolism. Animals. Adult mongrel dogs, 13.21 kg, prepared under aseptic surgical conditions with simple fistulae (for intravenous dosing) or Heidenhain pouches (for oral dosing) were used.[16]

Drug Administration and Sample Collection. 3-([*cyano*-^{14}C]Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**29**) was suspended in 0.4% methylcellulose at a concentration of 5 mg/mL. Three dogs were given a single intravenous dose of 0.2 mg/kg, and three were given a single oral dose of 4 mg/kg. Following drug treatment, plasma was collected from each animal at 5 (for the iv dose), 15, and 30 min and 1, 2, 3, and 4 h. Gastric juice was collected from the fistulae or pouches at 30-min intervals starting 1 h before and continuing to 4 h after treatment during intravenous infusion of histamine in saline (0.4 μg/kg per min).

Urine and feces were collected from each animal every 24 h for 7 days postdose.

Analysis of 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (27). Concentrations of **27** were measured by a specific HPLC method. Each plasma or gastric juice sample was diluted with an equivalent volume of water and then extracted with toluene. The organic layer was separated, toluene was evaporated, and the residue was reconstituted in the HPLC mobile phase and injected into the HPLC. The HPLC system consisted of a Waters Model 6000A pump, a Waters U6K injector, and a Waters Model 440 fixed-wavelength UV detector set to 280 nm. A Whatman ODS-2 reverse-phase column was used, and the mobile phase was methanol 1:0.5% aqueous phosphate buffer, pH 7.2 (3:1, v/v). Compound **27** was quantitated by the internal standard method; 3-(cyanomethyl)-2-methyl-8-[(4-*tert*-butylphenyl)methoxy]imidazo[1,2-*a*]pyridine[1] was the internal standard.

Analysis of Radioactivity. Radioactivity in plasma, gastric juice, urine, and fecal samples homogenized in water (3:1, v/w) was determined by mixing suitable aliquots with 15 mL of Scintisol and assaying for radioactivity in an Intertechnique SL liquid scintillation spectrometer. They were quench corrected by the internal standard method, with [^{14}C]hexadecane as the internal standard.

Isolation of Thiocyanate from Urine of Dogs Dosed with Labeled 3-(Cyanomethyl)-2-methyl-8-(phenylmethoxy)-imidazo[1,2-*a*]pyridine (28 and 29) and Labeled 3-Amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (41 and 42). Compounds **28** and **29** or compounds **41** and **42** were given orally to a single dog each (40 mg/kg), and urine was collected from the dogs for 48 h. Solid ammonium sulfate was added to the urine (1 g/mL), and the resulting mixture was extracted three times with ethyl acetate–2-propanol (1:1, v/v). The combined organic layers were concentrated and chromatographed on Whatman LK6DF TLC plates with 2-propanol–water–concentrated NH_4OH (8:1:1, v/v/v) as the mobile phase. Radioactive fractions were eluted with methanol and subjected to ion-exchange chromatography.[17] Thiocyanate eluting from the column was precipitated with silver oxide and analyzed by mass spectrometry[17] and ^{13}C magnetic resonance spectroscopy.

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Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, torsion angles, and displacements of atoms from selected least-squares planes, Figure 2, structure and solid-state conformation of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]-pyridine (**40**) as its hydrochloride salt, and Figure 3, crystal packing of 3-amino-2-methyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (**40**) as its hydrochloride in the unit cell (15 pages). Ordering information is given on any current masthead page.